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Environmental Pollutants, Occupational Exposures, and Liver Disease

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Abstract

Environmental pollutants significantly impact liver disease development, progression, and outcomes. This review examines the complex relationship between environmental exposures and liver pathology, from malignant conditions like hepatocellular carcinoma to steatotic and cholestatic liver diseases. Key environmental factors include air pollutants, volatile organic compounds, persistent organic pollutants, heavy metals, and per- and polyfluoroalkyl substances. These compounds can act through multiple mechanisms, including endocrine disruption, metabolic perturbation, oxidative stress, and direct hepatotoxicity. The impact of these exposures is often modified by factors such as sex, diet, and genetic predisposition. Recent research has revealed that even low-level exposures to certain chemicals can significantly affect liver health, particularly when combined with other risk factors. The emergence of exposomics as a research tool promises to enhance our understanding of how environmental factors influence liver disease. Importantly, exposure effects can vary by demographic and socioeconomic factors, highlighting environmental justice concerns. Implementation of this knowledge in clinical practice requires new diagnostic approaches, healthcare system adaptations, and increased awareness among medical professionals. In conclusion, this review provides a comprehensive examination of current evidence linking environmental exposures to liver disease and discusses implications for clinical practice and public health policy.

Graphical Abstract

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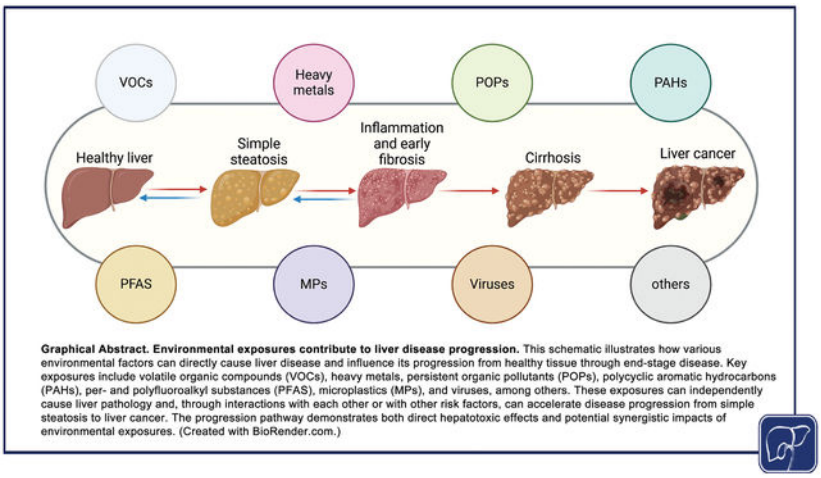

Graphical Abstract. Environmental exposures contribute to liver disease progression. This schematic illustrates how various environmental factors can directly cause liver disease and influence its progression from healthy tissue through end-stage disease. Key exposures include volatile organic compounds (VOCs), heavy metals, persistent organic pollutants (POPs), polycyclic aromatic hydrocarbons (PAHs), per- and polyfluoroalkyl substances (PFAS), microplastics (MPs), and viruses, among others. These exposures can independently cause liver pathology and, through interactions with each other or with other risk factors, can accelerate disease progression from simple steatosis to liver cancer. The progression pathway demonstrates both direct hepatotoxic effects and potential synergistic impacts of environmental exposures. (Created with BioRender.com.)

Lay Summary

Environmental chemicals found in air pollution, contaminated food and drinking water, and consumer products can harm the liver. These exposures may cause or worsen liver diseases depending on individual susceptibility. Understanding the effects of pollution on liver health has important implications for medical care and public health policy.

Keywords

environmental liver disease; occupational and environmental hepatology; toxicant-associated steatohepatitis; metabolism disrupting chemicals

Occupational and environmental hepatology is the medical subdiscipline that includes research, clinical evaluation, and treatment of patients with liver diseases associated with chemical exposures. The hepatotoxicity of occupational and environmental chemicals has long been documented. Classically described examples include acute liver failure related to solvent or mushroom poisoning, hepatic cholestasis related to consumption of contaminated food or cooking oil,[1,2] and liver cancer due to occupational vinyl chloride or environmental aflatoxin exposures.[3]

In 1962, Rachel Carson observed in *Silent Spring* that "As the tide of chemicals born of the industrial age has arisen to engulf our environment, a drastic change has come about in the nature of the most serious health problems."[4] Indeed, hepatology practice has seen a change in the incidence of specific liver diseases, most notably the observed dramatic increase in metabolic dysfunction-associated steatotic liver disease (MASLD), advanced fibrosis/cirrhosis, and hepatocellular carcinoma (HCC). Environmental pollutant exposures impact liver disease development, severity, and complications, and serve as disease modifiers.[5] For example, an astonishingly high 95.3% of National Health and Nutrition Examination Survey (NHANES) participants with advanced liver fibrosis had polychlorinated biphenyl (PCB) exposures in the highest exposure quartile.[6] Likewise, per- and polyfluoroalkyl substances (PFAS) exposures were positivelyassociated with adult MASLD and its severity using histologic or elastographic biomarkers.[7–12]

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The Agency for Toxic Substances and Disease Registry (ATSDR) maintains a list of substances commonly found at sites of National Priority (Superfund Sites). In 2022, this list identified 275 environmental chemicals posing the most significant potential threats to human health, with all top 10 highest priority chemicals associated with liver toxicity. The exposome is a paradigm-shifting concept in the environmental health sciences. It is the integrated compilation of environmental influences across the lifespan. These influences include chemical pollutants, diet, exercise, structural determinants of health, etc.[13] Exposomics, the study of the exposome, serves as the environmental counterpart to genomics.[13,14]

This review focuses specifically on occupational and environmental hepatology, considering exposomics as a research tool. We have actively investigated this area since 2010, reporting on the development of steatohepatitis in highly exposed vinyl chloride workers, termed toxicant-associated steatohepatitis (TASH). Research in chemical hepatocarcinogenesis spans nearly 50 years, following the 1974 identification of hepatic hemangiosarcoma in highly exposed polyvinyl chloride workers at a local chemical plant, and continues to the present day.[15,16]

Previous reviews have covered chemicals associated with liver disease and their proposed modes of action,[5,17–22] various conceptual frameworks,[13,14,23,24] and limited practice guidance.[25,26] However, many clinicians remain unaware of key concepts, and barriers persist in implementing new scientific knowledge in clinical practice. This review examines key environmental health science concepts impacting hepatology practice and evidence that common chronic liver diseases may be impacted by specific exposures (Tables 1 and 2), while identifying current scientific and clinical barriers.

Key Concepts in Environmental Health Science and Hepatotoxicity

The liver serves as the primary target organ for chemical exposures, largely due to its central role in xenobiotic metabolism. Primary routes of hepatotoxic chemical exposures include inhalation of air pollution and ingestion of contaminated food and drinking water.[27,28] Emerging data suggest that these exposures are not evenly distributed across the general population, with disproportionate impacts alongdemographic (e.g., race/ethnicity and sex), geographic, and socioeconomic lines, increasing risk for advanced liver fibrosis and HCC.[21,29] Environmental justice initiatives aim to address such inequitable risks. A positive recent example of environmental justice is the Promise to Address Comprehensive Toxics (PACT) Act of 2022 which addresses the toxic chemical exposures among United States military service personnel. Under this legislation, HCC is established as a presumptive health condition. More research is required on military exposures and MASLD, which has rapidly increased in active-duty service personnel and shows higher prevalence in Veterans than in the general population.[30,31]

Following absorption, pollutants undergo hepatic phase 1 and 2 metabolism. While some chemicals form hepatotoxic intermediates, others like PFAS undergo enterohepatic circulation, prolonging exposure. PFAS and other environmental chemicals such as PCBs and some toxic metals bioaccumulate in liver tissue, supporting their hepatotoxic potential.

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Chemical toxicity is often dose-dependent and can have a prolonged latency period, as demonstrated with vinyl chloride–related hepatic hemangiosarcomas.[16] Post-exposure risk for liver disease development appears dependent on race/ethnicity, sex, diet/nutritional status, and timing of the exposure in relation to windows of enhanced susceptibility during the lifespan.[16] For example, animal models demonstrate diet-dependent hepatotoxic effects for some chemicals which required a second hit such as hypercaloric diet to manifest toxicity.[17,32,33] This concept gains importance as environmental levels of some pollutants decrease while their clinical toxicity could increase due to dietary changes and rising obesity rates.

The developmental origins of health and disease (DOHaD) concept extends from maternal nutrition to environmental exposures affecting liver disease risk of the offspring.[34] Recent research shows that gestational PFAS exposures were associated with the changes in the metabolome and increased liver disease risk (primarily MASLD) in adolescent children.[35]

Beyond xenobiotic metabolism, the liver orchestrates intermediary metabolism in the body. Dysregulated hepatic intermediary metabolism has been associated with steatotic (e.g., altered lipid metabolism) and cholestatic (e.g., altered bile acid metabolism) liver diseases. Several key hypotheses refined over the last two decades have been proposed to explain the observed associations between pollutants and related endocrine, metabolic, and liver diseases. These include the endocrine disrupting chemical (EDC), obesogen, and metabolism disrupting chemical (MDC) hypotheses. EDCs, first described during 1991 Wingspread Conference, are currently defined by the Endocrine Society as “an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action.”[36] Over 1,000 potential EDCs have been identified and human exposure sources include industrial activity, food production (e.g., pesticides, food additives, and packaging materials), personal and home care products, as well as medical products and equipment (Fig. 1).[32,37]

A decade after the EDC hypothesis emerged, researchers first proposed chemical exposures’ potential role in weight gain and adiposity.[38] In 2006, the term environmental “obesogen” was introduced, supported by increasing experimental evidence.[39,40] While some laboratories investigated pollutants associated with obesity and dyslipidemia, our group began examining industrial chemicals (e.g., vinyl chloride) associated with altered liver lipid metabolism, hepatic steatosis, and TASH.[41] Recognizing the central theme of altered liver and systemic metabolism, the MDC hypothesis was proposed in 2016.[32] This unifying hypothesis states that environmental chemicals promote metabolic changes resulting in obesity, type 2 diabetes, or fatty liver,[32] along with associated conditions like metabolic syndrome, dyslipidemia, and hypertension. More recently, environmental chemical exposures including PCBs and pesticides were associated with human cholestatic liver diseases and disruption of bile acid and other metabolic pathways.[42,43] These reports suggest that MDCs can affect other liver diseases in addition to MASLD. The U.S. Environmental Protection Agency has recently implemented actions to limit exposure of population to MDCs, including certain PFAS and solvents. Further research is required to document the potential reversibility of established exposure-related chronic liver diseases following exposure reduction or elimination.

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Although mechanisms of hepatotoxic chemicals are well-established (Fig. 2), traditional methods cannot assess all 219 million registered chemical substances. Modern approaches combine mechanistic studies with epidemiological data to identify key characteristics of hepatotoxicants. To address this and other challenges, the key characteristic (KC) approach has been applied to provide the basis for a knowledge-based approach to evaluate mechanistic data rather than hypothesis-based approaches in toxicology (Fig. 2). Recently published KCs for EDCs,[44] MDCs,[45] carcinogens,[46] and human hepatotoxicants provide broad insight into hepatotoxic chemical actions.[24] These KCs include: reactivity of parent compound or metabolite, causes liver cell death, induces oxidative stress, triggers immune-mediated responses in liver, causes mitochondrial dysfunction, causes cholestasis, causes liver fibrosis, disrupts liver metabolism, etc. (Fig. 2).[24] Receptor-based mechanisms in chemical hepatotoxicity include ligand activation of transcription factors such as the aryl hydrocarbon receptor (by dioxins or dioxin-like molecules) or nuclear receptors such as the pregnane x receptor (by PFAS or PCBs).[17] These, and other indirect mechanisms (Fig. 2), including epigenomic modifications, lead to hepatic transcriptional reprogramming and liver disease risk.[17]

Malignant Liver Diseases

HCC stands as the sixth most common malignancy and the second most common cause of cancer-related fatalities worldwide. As the predominant form of liver cancer and one of the primary causes of cancer-related deaths globally,[47] its impact on global health is substantial, particularly given that non-resectable cases may have limited 5-year survival rates.[48] The complex relationship between environmental factors and liver cancers such as HCC and hepatic hemangiosarcoma has been revealed by occupational and environmental epidemiology studies. Environmental exposures can directly cause liver cancer through their genotoxicity, or indirectly cause liver cancer by promoting progressive liver fibrosis and cirrhosis.

Vinyl Chloride Exposure, Hepatic Hemangiosarcoma, and HCC

Hepatic hemangiosarcoma, a high-grade vascular tumor with a 3:1 male to female ratio, primarily affects those over 60 years of age. Despite constituting only 1 to 2% of liver tumors as the third most frequent primary hepatic tumor,[49] it carries particular significance due to its strong association with exposures and poor prognosis, with median survival of only 10 months even with surgical resection.[50] Several factors have been definitively linked to human hemangiosarcoma including rare genetic conditions, and exposures to radiation, thorotrast, or vinyl chloride (VC).[51,52] VC represents a widespread environmental contaminant, particularly as a solvent breakdown product in groundwater near military installations, garbage sites, and natural gas drilling locations. Its primary industrial use is in the rubber manufacturing sector as an intermediate monomer for polyvinyl chloride synthesis.[53] The connection between VC and liver angiosarcoma was first established in 1974 when multiple cases were identified among chemical workers at a VC polymerization company in Louisville, Kentucky.[15] Subsequently, additional cases were documented in Louisville and other locations, consistently associated with long-term VC exposure.[49,54–56] Other studies demonstrate associations between occupational VC exposures and HCC.[57] VC

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is classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1). More recent data suggest a potential role for environmental VC exposures and HCC. Liver cancer mortality rates show significant geographic variation in the United States. Texas, with an HCC incidence rate nearly double the national average, ranks third in the country. The state's extensive petrochemical industry, the second largest in the nation, suggests industrial air pollution may contribute to this elevated incidence.[58] Although one study suggested an association between residential toxic air exposures, including vinyl chloride, and Texas HCC, a follow-up study did not confirm this association.[29] More data are required.

Synergistic Effects of Environmental and Viral Factors: Aflatoxins, HBV, and HCC

The geographic distribution of HCC risk reflects the complex interplay of environmental factors, including endemic oncogenic viruses and dietary carcinogens, and HCC. Varying mechanisms of action (Fig. 2) and population-specific effects underscore the critical importance of considering both chemical exposure and demographic factors in comprehensive HCC risk assessment. Understanding these intricate interactions provides crucial insights into the environmental determinants of liver cancer development. The interaction between chronic hepatitis B infection (HBV) and chronic aflatoxin exposure provides a compelling example of this relationship.[59] Aflatoxins, carcinogenic mycotoxins produced by *Aspergillus* fungi, are widespread environmental contaminants in foods like nut crops or grains. Aflatoxins are IARC Group 1 carcinogens. The most toxic variant is aflatoxin B1 (AFB1), and its metabolites exhibit a range of biological activities, such as acute toxicity, teratogenicity, mutagenicity, and carcinogenicity. It has been well established that these compounds have been associated HCC in both humans and animals.[60,61] Particularly, AFM1, a measurable metabolite that serves as an index of chronic aflatoxin exposure, has been correlated with increased HCC incidence. Although Hispanic population showed lower AFM1 levels, their socioeconomic status may have influenced their exposure through consumption of lower-grade foods potentially contaminated with aflatoxins.[62] The synergistic relationship between HBV infection and aflatoxin exposure in liver cancer development was first documented in a Chinese cohort study.[63] Subsequent investigations in various contexts, particularly in African regions where HBV is endemic, have consistently confirmed this interaction. Evidence suggests that aflatoxins may enhance viral oncogenicity and potentially increase infection rates.[59] Even moderate aflatoxin exposures tripled the incidence of HCC development in a cohort of HBV-infected men.[64] Large-scale public health interventions aimed at reducing aflatoxin exposures and viral hepatitis infections promise to decrease the incidence of HCC related to these synergistic factors.[65] Proof-of-concept studies demonstrated the potential efficacy of pharmacologic and nutritional strategies that promoted the phase 2 metabolism of toxic aflatoxin metabolites in the chemoprevention of HCC.[66]

Additional Examples of Environmental Exposures and HCC

Select examples include benzo(a)pyrene (B[a]P), persistent organic pollutants, and metals. Data for these chemicals provide further proof of concept and support the need for future exposomics research in this area. B[a]P is an environmental toxicant commonly found in tobacco smoke, charcoal-grilled foods, engine exhaust, and contaminated air and water.

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B[a]P is an IARC Group 1 carcinogen. As a polycyclic aromatic hydrocarbon (PAH) formed during incomplete combustion of organic materials, B[a]P is a procarcinogen—meaning it requires metabolic activation to become carcinogenic.[67] It is activated by several cytochrome P450 enzymes and epoxide hydrolase to form the reactive metabolite, B[a]P diol epoxide (BPDE).[68] BPDE forms DNA adducts through covalent binding.[69] B[a]P promotes the development of reactive oxygen species (ROS) while simultaneously decreasing the activity of protective antioxidant enzymes like glutathione reductase.[68] The formation of ROS due to intrahepatic B[a]P triggers multiple pathological changes in the liver: it damages cellular components, disrupts normal metabolic processes, and creates an environment conducive to hepatocarcinogenesis.[70] In epidemiological studies done in Xiamen, China, significantly higher levels BPDE-DNA adducts were observed in patients with HCC. Elevated BPDE-DNA adducts also indicated increased HCC risk, showing it to be an independent risk factor for HCC.[69] Experimental studies demonstrate that B[a]P stimulated cell migration and enhanced angiogenesis, which are important HCC mechanisms.[67] In a murine HCC model, B[a]P exposure increased metastases and decreased survival.[71]

Several persistent organic pollutants (POPs) have been associated with HCC in epidemiologic studies. As thermodynamically stable molecules, POPs are resistant to degradation in the environment. These so-called “forever chemicals” bioaccumulate and oftentimes concentrate within the liver. PCBs are POPs and IARC Group 1 carcinogens. PCBs were manufactured for a variety of industrial educations before their use was banned approximately 40 years ago.[72] The carcinogenic potency of PCBs varies based on their chemical structure: higher chlorinated PCBs primarily promote cell proliferation, while lower chlorinated PCBs can form DNA-binding adducts.[73] PCBs have been associated with HCC in experimental models, with administration showing increased liver tumors in rats. These experimental findings align with human epidemiological data. For example, a population-based study in Northern California found that certain PCB congeners, such as those that are highly chlorinated, were associated with an increased risk of HCC.[74]

Pesticide exposures have been associated with human HCC.[75] Dichlorodiphenyltrichloroethane (DDT) is used as an insecticide and anti-malarial agent. It is an IARC Group 2A carcinogen (probably carcinogenic to humans), and it has been associated with incidence of liver cancer. The mode of carcinogenesis is primarily due to oxidative stress.[76] Animal studies have demonstrated that DDT promotes oxidative stress at both high and low doses, as evidenced by increased levels of 8-OHdG, an established marker of oxidative DNA damage.[77] These mechanistic findings are supported by population-based studies in China, where analyses of serum DDT levels revealed a 4-fold increase in HCC risk. The risk appears particularly pronounced in men, possibly due to DDT’s endocrine-disrupting properties.[78]

PFAS, another class of synthetic POPs, contain fluorinated carbon chains of variable lengths. PFAS have been widely used in nonstick coating applications (e.g., cookware, thermal insulation, electrical equipment).[79,80] PFAS are primarily ingested through contaminated drinking water or food and distribute either freely or bound to serum proteins.[81,82] Like other POPs, PFAS have long biological half-lives[83] and tend to bioaccumulate in liver.[84] Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are PFAS that were

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recently designated as human carcinogens by IARC (Groups 1 and 2a, respectively). A recently published nested case-control study demonstrated that elevated PFOS levels were associated with 4.5-fold increased risk of HCC.[85] Metabolomics analysis demonstrated that PFOS exposure was associated with alterations in amino acid and glycan biosynthesis pathways, which were also associated with HCC risk.[85]

Ranking first on ATSDR's Substance Priority List, arsenic is a metalloid and IARC Group 1 carcinogen that has been associated with human HCC.[86] Arsenic exposure in mouse models increased cancer growth and metastasis.[87] Interestingly, in humans the association between arsenic and liver cancer is stronger in females compared with males.[88] A recent geospatial study found variability in arsenic exposures along racial–ethnic and sex groups.[29] Arsenic exposures were positively associated with elevated HCC rates, and these rates varied by demographic variables.[88] Like aflatoxin, there appear to be environmental justice concerns for arsenic in liver cancer.

Non-malignant Liver Diseases

Metabolic Associated Steatotic Liver Disease (MASLD)

MASLD, formerly known as non-alcoholic fatty liver disease (NAFLD), affects approximately 30% of adults worldwide.[89] Characterized by excessive hepatic fat accumulation, MASLD is linked to metabolic abnormalities such as obesity and insulin resistance. The disease can progress from potentially reversible stages (steatosis and steatohepatitis) to more severe irreversible stages including fibrosis and cirrhosis if left untreated.[90] Disease progression is influenced by multiple factors including genetic predisposition, metabolic dys-regulation, and the exposome—the totality of environmental exposures throughout an individual's life (Fig. 2).[5] Environmental influences such as air pollutants have increasingly become the focus of environmental studies.[91,92] Emerging research continues to highlight the potential of environmental factors as key contributors to MASLD and its severity (Table 1).

Particulate Matter 2.5 ($PM_{2.5}$) and Air Pollution: $PM_{2.5}$ includes small (less than 2.5 microns) airborne particles released by anthropogenic sources (e.g., automobile emissions, wildfires, industrial combustion) and natural sources (e.g., dust storms, volcanic eruptions). Recent large environmental epidemiology studies reproducibly demonstrate the adverse human hepatic effects of $PM_{2.5}$ and related air pollutants. With sample sizes of up to 45M subjects, these include some of the largest environmental hepatology studies ever conducted.[93–100] Air pollution was associated with increased risk for incident MASLD and/or cirrhosis in longitudinal studies.[93,96–100] These exposures were associated with alterations in the circulating metabolome[98] and proteome.[99] These alterations mediated, in part, the observed associations between air pollution and MASLD. Other studies in young adults or Latino youth demonstrated PNPLA3-dependent associations between air pollution and liver stiffness, as well as air pollution-related excess MASLD risk associated with serum microRNA networks.[101,102] Longitudinal studies demonstrate that exposures to residential green and blue spaces decreased risk for incident MASLD or severe liver disease, and that this protective effect was mediated by reduction in $PM_{2.5}$ and other air pollutants.[96,97]

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The scientific understanding of the hepatic effects of air pollution is rapidly evolving and warrants continued attention.

Volatile Organic Compounds (VOCs): Originating from natural and artificial sources, VOCs are characterized by their limited water solubility and high volatility.[103] These compounds include known hepatotoxic substances such as perchloroethylene (PCE), trichloroethylene (TCE), and vinyl chloride (VC), which are present in various industrial and consumer products, including metal degreasing and dry-cleaning agents.[104,105] The health effects of VOCs extend beyond their carcinogenic properties, ranging from acute manifestations such as headaches and dizziness to chronic conditions including respiratory disease and cancer.[106]

VC exposure, which gained renewed attention following a 2023 train derailment and chemical spill,[107] exemplifies the complexities of VOC-induced liver injury. Recent experimental studies using various diet models demonstrate that VC induces hepatotoxicity at both high concentrations and at levels previously considered safe. When combined with a high fat diet, VC inhalation significantly exacerbated liver damage through altered mitochondrial function and increased ROS production.[53,103]

Clinical evidence supports these experimental findings. A study examining liver biopsies from VC-exposed workers found that 80% exhibited MASLD despite normal liver enzyme levels.[41] Sex-specific differences in VOC-related liver injury have been documented in both Canadian[108] and U.S. populations,[109] with recent clinical studies demonstrating significant associations between VOC exposure and MASLD development.[110] Additionally, studies on VOC-exposed e-waste dismantling workers have shown positive correlations between exposure and liver damage markers such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST).[92]

Persistent Organic Pollutants (POPs): POPs are synthetic polyhalogenated aromatic hydrocarbons resistant to biological, chemical, and photolytic degradation, resulting in environmental persistence.[111] These compounds accumulate in adipose tissue and disrupt endocrine, immune, and metabolic systems through xenobiotic receptor interactions.[32,112] Human exposure occurs primarily through ingestion of contaminated food, particularly high-fat animal products.[113]

PCBs, originally used as dielectric fluids, were first linked to liver damage during the “Yucheng” and “Yusho” poisoning incidents in the 1970s.[114,115] Studies of PCB-exposed populations have shown positive correlations between PCB body burdens and elevated liver enzymes (ALT, AST), cell death markers (CK18), and ultrasonography-diagnosed hepatic steatosis.[116–120] Recent studies have linked PCB levels in umbilical cord blood to elevated liver enzymes and circulating lipids in newborns.[121] Notably, prenatal exposure to PCBs including PCB118, PCB153, and PCB180 was associated with increased CK-18 levels in children.[122] Sex differences have been reported in PCB-exposed populations (“Yucheng” and “Yusho” cohorts), with females showing higher liver cancer mortality than males.[123,124]

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Dioxins, including polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like PCBs, are characterized by their aryl hydrocarbon receptor (AHR)-binding activity. High-level dioxin exposures involving Agent Orange exposure, PCB/PCDF-contaminated cooking oil in the Yucheng population, and the Seveso industrial explosion have been associated with increased liver cancer incidence and mortality.[124–128] Additionally, Tetrachlorodibenzo-p-Dioxin (TCDD) exposure resulted in increased prevalence of liver cirrhosis in Korean Vietnam Veterans.[27,126]

PCBs and dioxins contribute to liver disease as both endocrine and metabolic disruptors (EDCs and MDCs) through activation of hepatic receptors including AHR, constitutive androstane receptor (CAR), and pregnane-xenobiotic receptor (PXR).[129] These transcription factors regulate energy homeostasis through receptor–receptor crosstalk.[130] Moreover, PCBs interact with endobiotic receptors to modulate steatosis and bile acid homeostasis.[129]

As EDCs, these compounds disrupt thyroid and sex hormone receptors,[131] inhibit insulin production,[132] and alter endocrine hormone levels.[17,32,133] Recent studies have demonstrated additional mechanisms including gut microbiome alterations,[134] modification of liver epitranscriptomics,[135] and changes in RNA splicing[136] (Fig. 2). These effects are often exacerbated by lifestyle factors such as high caloric intake and alcohol consumption.[119]

Organochlorine pesticides, including DDT and its metabolites (e.g., dichlorodiphenyldichloroethylene, DDE), have been increasingly associated with liver disease. Organochlorine pesticides have been linked with elevated liver enzymes,[137,138] steatosis,[139] and altered lipid metabolism.[140,141] Sex-specific effects include β-hexachlorocyclohexane (β-HCH) and transnonachlor associations with elevated ALT in post-bariatric surgery females, while β-HCH, DDE, and hexachlorobenzene (HCB) showed stronger associations with transaminases in Brazilian males.[142,143] Prenatal exposures to DDT and DDE were associated with increased odds of liver injury.[122]

Emerging evidence links brominated flame retardants (BFRs) to hepatic abnormalities.[144–146] Analysis of NHANES data (2005–2016) showed positive associations between nine BFRs and elevated liver enzymes and MASLD risk scores, but not advanced fibrosis.[147] Novel BFRs like BTBPE have been associated with altered bilirubin levels.[148] BFRs act through PPAR α activation,[149] gut microbiome changes,[150] and inflammation and oxidative stress.[151]

Phthalates, though not traditional POPs, exhibit similar persistence and EDC activity.[152] Cross-sectional studies have shown associations between urinary Di(2-ethylhexyl) phthalate (DEHP) metabolites and metabolic syndrome in postmenopausal females, and linked diisononyl phthalate to MASLD diagnosed by elastography.[153]

Per- and Polyfluoroalkyl Substances (PFAS): The National Academies report on PFAS (2022) described evidence of association of PFAS and dyslipidemia (sufficient evidence) or liver enzyme alterations (limited or suggestive evidence).[154] This committee recommended that clinicians should offer serum PFAS testing to patients likely to

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have elevated exposures. Robust epidemiological studies have associated PFAS exposure to various deleterious impacts including hepatocellular apoptosis, increased liver injury biomarkers, and altered blood lipids.[155–158] Since the publication of the National Academies guidance, six cross-sectional studies investigated associations between PFAS and MASLD characterized by either liver histology[7,8] (n = 100–105 subjects all with MASLD), or FibroScan, investigating adult NHANES 2017–2018 participants (n = 696–1,400).[10–12,159] The liver histology studies found significant positive associations between serum PFAS and hepatic steatosis,[7,8] MASH,[8] and fibrosis.[7,8] Mechanistically, basic science research studies demonstrate that PFAS induce lipid accumulation and synthesis pathways while decreasing lipid export in hepatocytes. Further, serum PFAS were associated with alterations in the hepatic metabolome, including enrichment in pathways associated with MASLD (e.g., bile acids, sphingolipids, and glycerophospholipids).[8]

Recent manuscripts reported positive associations of PFAS with adult HCC or pediatric MASLD and altered metabolomes in these subjects with liver disease.[85,160] The four NHANES Fibro-Scan studies reported positive associations of PFASwith hepatic steatosis,[159] fibrosis (Liver Stiffness Measurement),[10,159] and MASLD.[11,12] More basic science, epidemiological work, and clinical research are required to further understand PFAS mechanisms and at-risk populations to propose guidelines of restricted use at the federal level and on clinical care.

Metals and Altered Metal Homeostasis: Heavy metals have deleterious effects on many organ systems, including the liver. Although some metals are required in trace amounts for the proper function of specific enzymes, others play no known role in normal biological function. Large epidemiological studies have revealed associations between MASLD and exposure to arsenic,[161] cadmium,[162–164] lead,[165,166] and mercury.[163,164] Among the essential metals, zinc and copper may protect against MASLD progression, given that a deficiency in these metals is associated with increased disease.[167,168] Alternatively, the essential metal iron is associated with MASLD when it is present at high concentrations in the liver or in circulation.[169–212]

Microplastics (MPs) and Plasticizers: MPs are fibers, spheres, and fragments of plastic particles less than 5 mm.[171] MPs are deliberately produced for use in medical devices, personal care items, cosmetics, cleaning products, and food packaging. They are also produced through environmental breakdown of larger plastics. Improper plastic disposal has led to increased MP abundance in the environment, impacting both aquatic and terrestrial life.[172] MPs have become ubiquitous globally, with detection in food and water.[173] Importantly, they have entered the food chain[174,175] and been detected in human, including stool, blood, breastmilk, saliva, liver and lungs.[176–181]

In humans MP exposure occurs primarily through ingestion, inhalation, and dermal contact.[175] Although human toxicity data remain limited, preclinical studies have demonstrated that MPs can induce inflammatory responses,[184] generate ROS,[185] and cause metabolic disorders.[186–190] Phthalates and bisphenol A (BPA) are common plasticizers used to enhance material flexibility and durability of plastics produced for building materials, medical devices, food packaging, cleaning materials, and children's toys.[191–193]

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Their widespread presence in dust and in the U.S. adult population has earned them the designation “everywhere chemicals.”[193–201] These compounds readily leach from plastics due to the absence of chemical bonds to the polymer matrix, leading to human exposure through ingestion, inhalation, and dermal contact.[191,202–205] Both phthalates and BPA are EDCs[206,207] and have been classified as obesogens.[212–214] Clinical studies have associated these compounds with type 2 diabetes, obesity, cardiovascular disorders, hypertension, liver injury, and MASLD.[199–201,210,211] Cross-sectional studies have shown associations between urinary metabolites and metabolic syndrome and MASLD.[155]

Polycyclic Aromatic Hydrocarbons (PAHs): PAHs are chemical compounds formed from incomplete combustion of coal, wood, and oil, as well as through cigarette smoking and charred meat. They exist ubiquitously in the environment and are frequently found in food, water, and air.[213] Analysis of PAH metabolites in urine from NHANES data (2003–2016) examined associations with liver function using ALT, AST, and Gamma-Glutamyl Transferase (GGT) as outcome variables. Results showed that for females, mixed PAH exposure was related to increased ALT levels. One specific PAH, 2-fluorene, showed associations with increased triglyceride and total cholesterol levels. These findings suggest PAHs may have toxic effects on the adolescent female liver, possibly mediated through inflammation and blood lipid alterations.[214]

Other Environmental Exposures: Modern agricultural practices have exposed populations to widespread pesticide residues through air, soil, water, and food,[215,216] leading to various hepatic and metabolic effects. Organophosphorus compounds and carbamates demonstrate particular toxicity—the former showing associations with obesity and type 2 diabetes in both human and rodent studies,[217–220] while carbamates like bendiocarb induce liver steatosis, necrosis, and fibrosis, with links to primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC).[43] Other pesticide classes show similar concerns: pyrethroids (e.g., bifenthrin) induce oxidative stress genes, and neonicotinoids like thiamethoxam promote dyslipidemia and MASLD.[221]

Glyphosate-based herbicides (GBH) represent a significant concern at human exposure levels. In rats, long-term GBH exposure causes liver congestion and necrosis in males and increased mortality in females,[222] while disrupting endocrine signaling and altering hepatic transcriptome profiles.[223,224] Clinical studies corroborate these findings—children aged 5 to 18 years with higher urinary concentrations of glyphosate and its degradation product AMPA show elevated liver transaminases and metabolic syndrome.[225]

Fungicides also demonstrate hepatotoxic effects through distinct mechanisms (Fig. 2). Triazoles like flutriafol impair mitochondrial function and induce lipid accumulation,[226] mancozeb exacerbates fatty acid–induced steatosis,[227] and famoxadone suppresses hepatic fatty acid β-oxidation while disrupting thyroid hormone signaling.[228]

Personal care products often contain heavy metals, endocrine-disrupting compounds, parabens (preservatives), bisphenols (plastic components), benzophenones (UV filters), and alkylphenol ethoxylates (emulsifiers).[229–233] These compounds demonstrate endocrine-disrupting properties and cause liver toxicity with extended daily use.[234] Synthetic

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fragrances can affect liver function through various mechanisms.[235–237] Alpha-iso-methylionone, a common fragrance ingredient, reduces AST levels and increases cholesterol, creatinine, and total protein in blood, along with increased liver weight.[238]

Climate Change and Algal Toxins: Climate change has increased harmful algal blooms containing microcystins (MCs). Human exposure occurs through contaminated food, water, or recreational activities.[239] MCs exhibit significant liver toxicity: acute exposure can lead to fatty liver disease and liver failure,[240] while chronic exposure causes sustained liver injury and inflammation. Population studies show a 0.3% increase in non-alcoholic liver disease risk for each 1% increase in algal bloom-affected county area.[241]

Alcohol-Associated Liver Disease (ALD)

Alcohol consumption remains one of the leading causes of liver disease worldwide, contributing substantially to liver-related morbidity and mortality.[242] Compared with MASLD, much less is known about the role of environmental exposures in ALD (Table 2). Toxic chemicals including PAHs have been shown to variably contaminate alcoholic beverages.[243] Moreover, recent epidemiological data from two large cohort studies (n = 90,086 to 456,678 subjects) indicate that the increased risk for MASLD associated with air pollution and PM2.5 exposures was more pronounced in alcohol drinkers.[93,94] Likewise, PFAS exposures were associated with steatotic liver disease in alcohol drinkers but not in non-drinkers.[12] Similar to ethanol, certain pollutants including VOCs are metabolized by CYP2E1 to form toxic intermediates, suggesting that chronic ethanol consumption may enhance pollutant toxicity by increasing CYP2E1 levels and generating their toxic metabolites. Supporting this concept, VC workers who consumed alcohol showed increased risk for cirrhosis and liver cancer than those that did not drink alcohol.[244] This CYP2E1-mediated interaction was confirmed in experimental models, where ethanol exposure increased the hepatotoxicity of 1,2 dichloroethane, which is a chemical intermediate used in VC production.[245] Animal co-exposure models have revealed additional mechanisms by which environmental pollutants exacerbate experimental ALD, including altered zinc-dependent transcription factor function associated with PCBs,[246,247] mitochondrial dysfunction associated with the Northern contaminant mixture,[248] oxidative stress associated with particulate matter,[249] and activation of inflammatory mechanisms associated with Gulf War Illness related chemicals.[250] Collectively, these and other data suggest an under-recognized role for environmental exposures in ALD. Further research is required to elucidate the interactions between environmental pollutants and alcohol-associated hepatitis and cirrhosis as well as MetALD.

Viral Hepatitis

Relatively little is known about the potential disease-modifying effects of environmental chemicals on viral hepatitis, and more research in this area is required. However, viral hepatitis does appear to increase the risk of liver cancer and/or cirrhosis related to aflatoxin or VC exposures.[59,244] The environmental aldehyde, acrolein, inhibited host interferon signaling and increased viral load in the HCV replicon system.[251] However, the potential clinical impact of this observation is unknown.

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Cholestatic Liver Disease

Cholestatic liver disease is characterized by impaired bile flow through the biliary system. Published environmental health data exist for PBC and PSC. Although increased PBC risk in individuals with family history is well established, genetic factors alone do not explain all cases. More classically described environmental factors associated with PBC include frequent urinary tract infections, nail polish use, and cigarette smoking.[252,253] Some of these have been proposed to explain the higher prevalence of PBC in women. Chemical pollutant exposures have also been associated with PBC. In the United Kingdom, PBC incidence was higher in urban areas with histories of coal mining and high levels of cadmium. In New York, a higher incidence of PBC, but not PSC, was reported in zip codes that either contained or were adjacent to superfund toxic waste sites.[254,255] Recently, two important manuscripts, including a multinational comparison study, were published which applied integrative exposomics and metabolomics approaches to subjects with PBC or PSC compared with controls.[42,43] Multi-omics analyses were performed in plasma (PBC and PSC patients) or bile (PSC patients only).[42,43] A total of 12 environmental pollutants in plasma were associated with PSC, and 8 were associated with PBC. Some of these exposures were associated with metabolic pathways linked to the pathogenesis of cholestatic liver diseases including bile acid metabolism. Pollutants detected in the bile of PSC patients varied by country.[42] PBCs in bile were associated with metabolic disruption, including bile acid metabolism, in these subjects.[42] These results demonstrate the power of the exposomics approach in hepatology.

Clinical Implementation and Knowledge Gaps

It is time to implement this knowledge in patient care, health care systems, and at population health levels. At the patient level, approaches to reduce personal exposures can be already implemented.[256] These approaches broadly include specific modifications to limit exposures encountered through some personal care and hygiene products, consumables, home and garden, etc.[256] Clinical proof-of-concept studies have demonstrated potential effectiveness of pharmacologic and dietary interventions that increase fecal or urinary elimination of some pollutants to decrease burden.[257–260] Some patients may require specific risk-based laboratory exposure assessments. In its recent clinical guidance on PFAS, the National Academies recommended that clinicians should offer serum PFAS testing to patients with defined risk factors for PFAS exposures.[261] Reference laboratories as well as test and CPT codes were suggested. Specific clinical action items were recommended based on these test results, although none of the action items was related to liver disease.[261] For workers at risk for occupational liver disease, a diagnostic algorithm has been proposed and management guidance published.[26] However, health care providers require education and guidance on environmental hepatology. We urge the medical societies publishing clinical guidelines on liver diseases to include environmental health considerations. The Veteran’s Health Administration has already implemented changes demonstrating that health care systems can act on environmental health issues. New liver disease nomenclature, diagnosis, and billing codes may be required for full implementation within the electronic medical record systems used by healthcare systems. Nomenclature remains problematic as evidenced by the fact that environmental exposures were not considered in the recent Delphi consensus statement on steatotic liver disease (SLD) nomenclature,[262] even though TASH was described 15 years

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ago.[41] The US Federal government has recently taken actions aimed at reducing specific toxic exposures that have been associated with liver disease (e.g., some PFAS and solvents). Leadership is required from the relevant medical societies in terms ofenvironmental health advocacy impacting government, commercial diagnostic laboratories, and payers. Despite considerable advances, key scientific knowledge gaps remain. Longitudinal data are required on pollution and fibrosis progression, HCC development, response to therapy, and clinical outcomes. More research is required on the interactions between gene and environment impacting liver diseases, the exposome, and on the diagnoses with currently limited data.

Conclusions

The evidence supports that patients and providers should care about the occupational and environmental factors influencing liver diseases. Pollution is a disease modifier associated with the development, severity, and complications of liver disease. It is now time to begin implementation of environmental health science in hepatology practice. Leadership from medical societies, health care systems, payers, and government are required to remove barriers impacting the translation of knowledge to clinical practice. The exposome is an important new concept in hepatology which could be incorporated in a future precision medicine approach to liver health.

Conflict of Interest

The authors have no relevant competing interests to declare. The University of Louisville has received unrelated research support on Dr. Cave's behalf from Akero Therapeutics, the DURECT Corporation, Intercept Pharmaceuticals, and CymaBay Therapeutics/Gilead Sciences. Dr. Cave has participated on unrelated advisory and/or speakers boards for Madrigal Pharmaceuticals, Gilead Sciences, Intercept Pharmaceuticals, and Ipsen Global.

References

1. Kopelman H, Robertson MH, Sanders PG, Ash I. The Epping jaundice. BMJ 1966;1(5486):514–516 [PubMed: 5902696]
2. Solis-Herruzo JA, Vidal JV, Colina F, Castellano G, Muñoz-Yagüe MT, Morillas JD. Clinico-biochemical evolution and late hepatic lesions in the toxic oil syndrome. Gastroenterology 1987;93(03): 558–568 [PubMed: 3609665]
3. Benkerroum N. Retrospective and prospective look at aflatoxin research and development from a practical standpoint. Int J Environ Res Public Health 2019;16(19):16
4. Carson RL. Silent Spring. New York Houghton Mifflin Company/Riverside Press; 1962
5. Beier JI, Arteel GE. Environmental exposure as a risk-modifying factor in liver diseases: knowns and unknowns. Acta Pharm Sin B 2021;11(12):3768–3778 [PubMed: 35024305]
6. Ma N, Yip R, Lewis S, et al. Environmental exposures are important risk factors for advanced liver fibrosis in African American adults. JHEP Rep Innov Hepatol 2023;5(04):100696
7. David N, Antignac JP, Roux M, et al. Associations between perfluoroalkyl substances and the severity of non-alcoholic fatty liver disease. Environ Int 2023;180:108235 [PubMed: 37776622]
8. Sen P, Qadri S, Luukkonen PK, et al. Exposure to environmental contaminants is associated with altered hepatic lipid metabolism in non-alcoholic fatty liver disease. J Hepatol 2022;76(02): 283–293 [PubMed: 34627976]
9. Samala N, Kulkarni M, Lele RS, et al. Associations between per- and polyfluoroalkyl substance exposures and metabolic dysfunction associated steatotic liver disease (MASLD) in adult National Health and Nutrition Examination Survey 2017 to 2018. Toxicol Sci 2024;202(01):142–151 [PubMed: 39150893]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

10. Cheng W, Li M, Zhang L, et al. Close association of PFASs exposure with hepatic fibrosis than steatosis: evidences from NHANES 2017–2018. Ann Med 2023;55(01):2216943 [PubMed: 37323015]
11. Zhang Y, Zhang M, Jiang S, et al. Associations of perfluoroalkyl substances with metabolic-associated fatty liver disease and non-alcoholic fatty liver disease: NHANES 2017–2018. Cancer Causes Control 2024;35(09):1271–1282 [PubMed: 38764062]
12. Zhang X, Zhao L, Ducatman A, et al. Association of per- and polyfluoroalkyl substance exposure with fatty liver disease risk in US adults. JHEP Rep Innov Hepatol 2023;5(05):100694
13. Barouki R, Samson M, Blanc EB, et al. The exposome and liver disease—how environmental factors affect liver health. J Hepatol 2023;79(02):492–505 [PubMed: 36889360]
14. Cheung AC, Walker DI, Juran BD, Miller GW, Lazaridis KN. Studying the exposome to understand the environmental determinants of complex liver diseases. Hepatology 2020;71(01): 352–362 [PubMed: 31701542]
15. Creech JL Jr, Johnson MN. Angiosarcoma of liver in the manufacture of polyvinyl chloride. J Occup Med 1974;16(03):150–151 [PubMed: 4856325]
16. Guardiola JJ, Hardesty JE, Beier JI, Prough RA, McClain CJ, Cave MC. Plasma metabolomics analysis of polyvinyl chloride workers identifies altered processes and candidate biomarkers for hepatic hemangiosarcoma and its development. Int J Mol Sci 2021;22 (10):22
17. Wahlang B, Jin J, Beier JI, et al. Mechanisms of environmental contributions to fatty liver disease. Curr Environ Health Rep 2019;6(03):80–94 [PubMed: 31134516]
18. VoPham T Environmental risk factors for liver cancer and nonalcoholic fatty liver disease. Curr Epidemiol Rep 2019;6 (01):50–66 [PubMed: 31080703]
19. Costello E, Rock S, Stratakis N, et al. Exposure to per- and polyfluoroalkyl substances and markers of liver injury: a systematic review and meta-analysis. Environ Health Perspect 2022;130(04):46001 [PubMed: 35475652]
20. Fritsche K, Ziková-Kloas A, Marx-Stoelting P, Braeuning A. Metabolism-disrupting chemicals affecting the liver: screening, testing, and molecular pathway identification. Int J Mol Sci 2023;24(03):24
21. Erkekoglu P, Oral D, Chao MW, Kocer-Gumusel B. Hepatocellular carcinoma and possible chemical and biological causes: a review. J Environ Pathol Toxicol Oncol 2017;36(02):171–190 [PubMed: 29199597]
22. Lang AL, Beier JI. Interaction of volatile organic compounds and underlying liver disease: a new paradigm for risk. Biol Chem 2018;399(11):1237–1248 [PubMed: 29924722]
23. Angrish MM, Kaiser JP, McQueen CA, Chorley BN. Tipping the balance: hepatotoxicity and the 4 apical key events of hepatic steatosis. Toxicol Sci 2016;150(02):261–268 [PubMed: 26980302]
24. Rusyn I, Arzuaga X, Cattley RC, et al. Key characteristics of human hepatotoxicants as a basis for identification and characterization of the causes of liver toxicity. Hepatology 2021;74(06): 3486–3496 [PubMed: 34105804]
25. Kanwal F, Neuschwander-Tetri BA, Loomba R, Rinella ME. Metabolic dysfunction-associated steatotic liver disease: update and impact of new nomenclature on the American Association for the Study of Liver Diseases practice guidance on nonalcoholic fatty liver disease. Hepatology 2024;79(05):1212–1219 [PubMed: 38445559]
26. European Association for the Study of the Liver. EASL clinical practice guideline: occupational liver diseases. J Hepatol 2019; 71(5):1022–1037 [PubMed: 31540728]
27. Zheng S, Yang Y, Wen C, et al. Effects of environmental contaminants in water resources on nonalcoholic fatty liver disease. Environ Int 2021;154:106555 [PubMed: 33857709]
28. Dolce A, Della Torre S. Sex, nutrition, and NAFLD: relevance of environmental pollution. Nutrients 2023;15(10):15
29. Oluyomi AO, Thrift AP, Olayode A, Symanski E, Roy H, El-Serag HB. Race/ethnicity and sex differences in the association between area-level arsenic exposure concentration and hepatocellular carcinoma (HCC) incidence rates in Texas. An ecological study. Environ Res 2024;240(Pt 2):117538 [PubMed: 37926230]
30. Mooney BL. Incidence of nonalcoholic fatty liver disease rises quickly in U.S. military. In: Mooney BL, ed. 2019 Compendium of Federal Medicine. 2019:33–35

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

31. Thrift AP, Nguyen TH, Pham C, et al. The prevalence and determinants of NAFLD and MAFLD and their severity in the VA primary care setting. Clin Gastroenterol Hepatol 2023;21(05): 1252–1260.e5 [PubMed: 35811043]
32. Heindel JJ, Blumberg B, Cave M, et al. Metabolism disrupting chemicals and metabolic disorders. Reprod Toxicol 2017;68:3–33 [PubMed: 27760374]
33. Lang AL, Chen L, Poff GD, et al. Vinyl chloride dysregulates metabolic homeostasis and enhances diet-induced liver injury in mice. Hepatol Commun 2018;2(03):270–284 [PubMed: 29507902]
34. Barker DJ. The origins of the developmental origins theory. J Intern Med 2007;261(05):412–417 [PubMed: 17444880]
35. Stratakis N, VConti D, Jin R, et al. Prenatal exposure to perfluoroalkyl substances associated with increased susceptibility to liver injury in children. Hepatology 2020;72(05):1758–1770 [PubMed: 32738061]
36. Zoeller RT, Brown TR, Doan LL, et al. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. Endocrinology 2012;153(09): 4097–4110 [PubMed: 22733974]
37. Sargis RM, Simmons RA. Environmental neglect: endocrine disruptors as underappreciated but potentially modifiable diabetes risk factors. Diabetologia 2019;62(10):1811–1822 [PubMed: 31451869]
38. Baillie-Hamilton PF. Chemical toxins: a hypothesis to explain the global obesity epidemic. J Altern Complement Med 2002;8(02): 185–192 [PubMed: 12006126]
39. Grün F, Blumberg B. Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. Endocrinology 2006;147(06):S50–S55 [PubMed: 16690801]
40. Heindel JJ, Howard S, Agay-Shay K, et al. Obesity II: establishing causal links between chemical exposures and obesity. Biochem Pharmacol 2022;199:115015 [PubMed: 35395240]
41. Cave M, Falkner KC, Ray M, et al. Toxicant-associated steatohepatitis in vinyl chloride workers. Hepatology 2010;51(02): 474–481 [PubMed: 19902480]
42. Grant CW, Juran BD, Ali AH, et al. Environmental chemicals and endogenous metabolites in bile of USA and Norway patients with primary sclerosing cholangitis. Exposome 2023;3(01):osac011
43. Walker DI, Juran BD, Cheung AC, et al. High-resolution exposomics and metabolomics reveals specific associations in cholestatic liver diseases. Hepatol Commun 2022;6(05):965–979 [PubMed: 34825528]
44. La Merrill MA, Vandenberg LN, Smith MT, et al. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nat Rev Endocrinol 2020;16(01):45–57 [PubMed: 31719706]
45. La Merrill MA, Smith MT, McHale CM, et al. Consensus on the key characteristics of metabolism disruptors. Nat Rev Endocrinol 2024. Epub ahead of print. Doi: 10.1038/s41574-024-01059-8
46. Smith MT, Guyton KZ, Gibbons CF, et al. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect 2016;124(06):713–721 [PubMed: 26600562]
47. Sagnelli E, Macera M, Russo A, Coppola N, Sagnelli C. Epidemiological and etiological variations in hepatocellular carcinoma. Infection 2020;48(01):7–17 [PubMed: 31347138]
48. Jemal A, Ward EM, Johnson CJ, et al. Annual report to the nation on the status of cancer, 1975–2014, featuring survival. J Natl Cancer Inst 2017;109(09):109
49. Block JB. Angiosarcoma of the liver following vinyl chloride exposure. JAMA 1974;229(01):53–54 [PubMed: 4406736]
50. Mani H, Van Thiel DH. Mesenchymal tumors of the liver. Clin Liver Dis 2001;5(01):219–257, viii [PubMed: 11218917]
51. Cohen SM, Storer RD, Criswell KA, et al. Hemangiosarcoma in rodents: mode-of-action evaluation and human relevance. Toxicol Sci 2009;111(01):4–18 [PubMed: 19525443]
52. Yonemori K, Tsuta K, Ando M, et al. Contrasting prognostic implications of platelet-derived growth factor receptor-β and vascular endothelial growth factor receptor-2 in patients with angiosarcoma. Ann Surg Oncol 2011;18(10):2841–2850 [PubMed: 21409488]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

53. Liu S, He L, Bannister OB, et al. Western diet unmasks transient low-level vinyl chloride-induced tumorigenesis; potential role of the (epi-)transcriptome. Toxicol Appl Pharmacol 2023; 468:116514 [PubMed: 37061008]
54. Falk H, Creech JL Jr, Heath CW Jr, Johnson MN, Key MM. Hepatic disease among workers at a vinyl chloride polymerization plant. JAMA 1974;230(01):59–63 [PubMed: 4547220]
55. Spirtas R, Kaminski R. Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers. 1977 update of the NIOSH register. J Occup Med 1978;20(06):427–429 [PubMed: 566788]
56. Lee FI, Harry DS. Angiosarcoma of the liver in a vinyl-chloride worker. Lancet 1974;1(7870):1316–1318 [PubMed: 4134297]
57. Fedeli U, Girardi P, Gardiman G, et al. Mortality from liver angiosarcoma, hepatocellular carcinoma, and cirrhosis among vinyl chloride workers. Am J Ind Med 2019;62(01):14–20 [PubMed: 30474170]
58. Cicalese L, Raun L, Shirafkan A, et al. An ecological study of the association between air pollution and hepatocellular carcinoma incidence in Texas. Liver Cancer 2017;6(04):287–296 [PubMed: 29234632]
59. Mouchtaris Michailidis T, De Saeger S, Khoueiry R, et al. The interplay of dietary mycotoxins and oncogenic viruses toward human carcinogenesis: a scoping review. Crit Rev Food Sci Nutr 2024:1–19. Epub ahead of print. Doi: 10.1080/10408398.2024.2414828
60. Cao W, Yu P, Yang K, Cao D. Aflatoxin B1: metabolism, toxicology, and its involvement in oxidative stress and cancer development. Toxicol Mech Methods 2022;32(06):395–419 [PubMed: 34930097]
61. Liu Y, Chang CC, Marsh GM, Wu F. Population attributable risk of aflatoxin-related liver cancer: systematic review and meta-analysis. Eur J Cancer 2012;48(14):2125–2136 [PubMed: 22405700]
62. Johnson NM, Qian G, Xu L, et al. Aflatoxin and PAH exposure biomarkers in a U.S. population with a high incidence of hepatocellular carcinoma. Sci Total Environ 2010;408(23):6027–6031 [PubMed: 20870273]
63. Ross RK, Yuan JM, Yu MC, et al. Urinary aflatoxin biomarkers and riskof hepatocellular carcinoma. Lancet 1992;339(8799):943–946 [PubMed: 1348796]
64. Ming L, Thorgeirsson SS, Gail MH, et al. Dominant role of hepatitis B virus and cofactor role of aflatoxin in hepatocarcinogenesis in Qidong, China. Hepatology 2002;36(05):1214–1220 [PubMed: 12395332]
65. Sun Z, Chen T, Thorgeirsson SS, et al. Dramatic reduction of liver cancer incidence in young adults: 28 year follow-up of etiological interventions in an endemic area of China. Carcinogenesis 2013; 34(08):1800–1805 [PubMed: 23322152]
66. Kensler TW, Egner PA, Wang JB, et al. Chemoprevention of hepatocellular carcinoma in aflatoxin endemic areas. Gastroenterology 2004;127(5, Suppl 1):S310–S318 [PubMed: 15508099]
67. Ba Q, Li J, Huang C, et al. Effects of benzo[a]pyrene exposure on human hepatocellular carcinoma cell angiogenesis, metastasis, and NF-κB signaling. Environ Health Perspect 2015;123(03): 246–254 [PubMed: 25325763]
68. Bukowska B, Mokra K, Michałowicz J. Benzo[*a*]pyrene—environmental occurrence, human exposure, and mechanisms of toxicity. Int J Mol Sci 2022;23(11):23
69. Su Y, Zhao B, Guo F, et al. Interaction of benzo[a]pyrene with other risk factors in hepatocellular carcinoma: a case-control study in Xiamen, China. Ann Epidemiol 2014;24(02):98–103 [PubMed: 24480391]
70. Yang Y, Jin M, Meng Y, et al. Involvement and targeted intervention of benzo(a)pyrene-regulated apoptosis related proteome modification and muti-drug resistance in hepatocellular carcinoma. Cell Death Dis 2023;14(04):265 [PubMed: 37041133]
71. Ge Y, Gu P, Wang W, et al. Benzo[a]pyrene stimulates miR-650 expression to promote the pathogenesis of fatty liver disease and hepatocellular carcinoma via SOCS3/JAK/STAT3 cascades. J Mol Cell Biol 2021;13(08):556–564 [PubMed: 34450627]
72. Montano L, Pironti C, Pinto G, et al. Polychlorinated biphenyls (PCBs) in the environment: occupational and exposure events, effects on human health and fertility. Toxics 2022;10(07):10 [PubMed: 35051052]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

73. Ludewig G, Robertson LW. Polychlorinated biphenyls (PCBs) as initiating agents in hepatocellular carcinoma. Cancer Lett 2013; 334(01):46–55 [PubMed: 23211541]
74. Niehoff NM, Zabor EC, Satagopan J, et al. Prediagnostic serum polychlorinated biphenyl concentrations and primary liver cancer: a case-control study nested within two prospective cohorts. Environ Res 2020;187:109690 [PubMed: 32474310]
75. Saad-Hussein A, Beshir S, Taha MM, et al. Early prediction of liver carcinogenicity due to occupational exposure to pesticides. Mutat Res Genet Toxicol Environ Mutagen 2019;838:46–53 [PubMed: 30678827]
76. Harada T, Takeda M, Kojima S, Tomiyama N. Toxicity and carcinogenicity of dichlorodiphenyltrichloroethane (DDT). Toxicol Res 2016;32(01):21–33 [PubMed: 26977256]
77. Kushida M, Sukata T, Uwagawa S, et al. Low dose DDT inhibition of hepatocarcinogenesis initiated by diethylnitrosamine in male rats: possible mechanisms. Toxicol Appl Pharmacol 2005;208 (03):285–294 [PubMed: 15885732]
78. Persson EC, Graubard BI, Evans AA, et al. Dichlorodiphenyltrichloroethane and risk of hepatocellular carcinoma. Int J Cancer 2012;131(09):2078–2084 [PubMed: 22290210]
79. PFAS Explained. United States Environmental Protection Agency. Accessed at: https://www.epa.gov/pfas/pfas-explained
80. Glüge J, Scheringer M, Cousins IT, et al. An overview of the uses of per- and polyfluoroalkyl substances (PFAS). Environ Sci Process Impacts 2020;22(12):2345–2373 [PubMed: 33125022]
81. Forsthuber M, Kaiser AM, Granitzer S, et al. Albumin is the major carrier protein for PFOS, PFOA, PFHxS, PFNA and PFDA in human plasma. Environ Int 2020;137:105324 [PubMed: 32109724]
82. Fischer FC, Ludtke S, Thackray C, et al. Binding of per- and polyfluoroalkyl substances (PFAS) to serum proteins: implications for toxicokinetics in humans. Environ Sci Technol 2024;58 (02):1055–1063 [PubMed: 38166384]
83. Lin PD, Cardenas A, Hauser R, et al. Temporal trends of concentrations of per- and polyfluoroalkyl substances among adults with overweight and obesity in the United States: results from the Diabetes Prevention Program and NHANES. Environ Int 2021;157:106789 [PubMed: 34333293]
84. Xing Y, Zhou Y, Zhang X, et al. The sources and bioaccumulation of per- and polyfluoroalkyl substances in animal-derived foods and the potential risk of dietary intake. Sci Total Environ 2023; 905:167313 [PubMed: 37742961]
85. Goodrich JA, Walker D, Lin X, et al. Exposure to perfluoroalkyl substances and risk of hepatocellular carcinoma in a multiethnic cohort. JHEP Rep Innov Hepatol 2022;4(10):100550
86. Liu J, Waalkes MP. Liver is a target of arsenic carcinogenesis. Toxicol Sci 2008;105(01):24–32 [PubMed: 18566022]
87. Smith AH, Hopenhayn-Rich C, Bates MN, et al. Cancer risks from arsenic in drinking water. Environ Health Perspect 1992; 97:259–267 [PubMed: 1396465]
88. Chiu HF, Ho SC, Wang LY, Wu TN, Yang CY. Does arsenic exposure increase the risk for liver cancer? J Toxicol Environ Health A 2004;67(19):1491–1500 [PubMed: 15371225]
89. Chan WK, Chuah KH, Rajaram RB, Lim LL, Ratnasingam J, Vethakkan SR. Metabolic dysfunction-associated steatotic liver disease (MASLD): a state-of-the-art review. J Obes Metab Syndr 2023;32(03):197–213 [PubMed: 37700494]
90. Phoolchund AGS, Khakoo SI. MASLD and the development of HCC: pathogenesis and therapeutic challenges. Cancers (Basel) 2024;16(02):16
91. Ya P, Xu H, Ma Y, et al. Liver injury induced in Balb/c mice by $PM_{2.5}$ exposure and its alleviation by compound essential oils. Biomed Pharmacother 2018;105:590–598 [PubMed: 29890467]
92. Yu H, Ma J, Chen D, Gao Y, Li G, An T. Associations between inhalation of typical volatile and semi-volatile organic compounds in e-waste dismantling workers with liver function damage. J Hazard Mater 2024;464:133004 [PubMed: 37984141]
93. Li FR, Liao J, Zhu B, et al. Long-term exposure to air pollution and incident non-alcoholic fatty liver disease and cirrhosis: a cohort study. Liver Int 2023;43(02):299–307 [PubMed: 36069651]
94. Guo B, Guo Y, Nima Q, et al. ; China Multi-Ethnic Cohort (CMEC) collaborative group. Exposure to air pollution is associated with an increased risk of metabolic dysfunction-associated fatty liver disease. J Hepatol 2022;76(03):518–525 [PubMed: 34883157]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

95. Ji W, Cheng Y, Tang S, et al. Exposure to ambient air pollution and metabolic dysfunction-associated fatty liver disease: findings from over 2.7 million adults in Northwestern China. Ecotoxicol Environ Saf 2024;272:116109 [PubMed: 38364762]

96. Ye Z, Liu M, He P, et al. Various ambient air pollutants, residential green spaces, fibrosis 4 scores, genetic susceptibility, and risk of severe liver disease. Ecotoxicol Environ Saf 2023;263:115246 [PubMed: 37453269]

97. Liu M, Yang S, Ye Z, et al. Residential green and blue spaces with nonalcoholic fatty liver disease incidence: mediating effect of air pollutants. Ecotoxicol Environ Saf 2023;264:115436 [PubMed: 37672940]

98. Ran S, Zhang J, Tian F, et al. Association of metabolic signatures of air pollution with MASLD: observational and Mendelian randomization study. J Hepatol 2024:S0168–8278(24)02573-X. Epub ahead of print. Doi: 10.1016/j.jhep.2024.09.033

99. Aimuzi R, Xie Z, Qu Y, Luo K, Jiang Y. Proteomic signatures of ambient air pollution and risk of non-alcoholic fatty liver disease: a prospective cohort study in the UK Biobank. Sci Total Environ 2024;957:177529 [PubMed: 39547383]

100. VoPham T, Kim NJ, Berry K, Mendoza JA, Kaufman JD, Ioannou GN. $PM_{2.5}$ air pollution exposure and nonalcoholic fatty liver disease in the Nationwide Inpatient Sample. Environ Res 2022;213:113611 [PubMed: 35688225]

101. Patterson WB, Holzhausen E, Chalifour B, et al. Exposure to ambient air pollutants, serum miRNA networks, lipid metabolism, and non-alcoholic fatty liver disease in young adults. Ecotoxicol Environ Saf 2023;264:115486 [PubMed: 37729806]

102. Schenker RB, Machle CJ, Allayee H, et al. Ambient air pollution exposure is associated with liver fat and stiffness in Latino youth with a more pronounced effect in those with PNPLA3 genotype and more advanced liver disease. Ecotoxicol Environ Saf 2024; 286:117234 [PubMed: 39454357]

103. Schnegelberger RD, Lang AL, Arteel GE, Beier JI. Environmental toxicant-induced maladaptive mitochondrial changes: a potential unifying mechanism in fatty liver disease? Acta Pharm Sin B 2021;11(12):3756–3767 [PubMed: 35024304]

104. Case Studies on Safer Alternatives for Solvent Degreasing Applications. United States Environmental Protection Agency. Available at: https://www.epa.gov/p2/case-studies-safer-alternatives-sol-vent-degreasing-applications

105. Risk Management for Perchloroethylene (PCE). United States Environmental Protection Agency. Available at: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-management-perchloroethylene-pce

106. Vipin Soni PS. Shree Venu & Goel Varun Effects of VOCs on Human Health. In, Air Pollution and Control. Springer Singapore 2018:119–142

107. Sun W The devastating health consequences of the Ohio derailment: a closer look at the effects of vinyl chloride spill. Int J Environ Res Public Health 2023;20(06):20

108. Cakmak S, Cole C, Hebbern C, Andrade J, Dales R. Associations between blood volatile organic compounds, and changes in hematologic and biochemical profiles, in a population-based study. Environ Int 2020;145:106121 [PubMed: 32947160]

109. Wahlang B, Gao H, Rai SN, et al. Associations between residential volatile organic compound exposures and liver injury markers: the role of biological sex and race. Environ Res 2023;221:115228 [PubMed: 36610539]

110. Duan X, Chen Z, Liao J, et al. The association analysis between exposure to volatile organic compounds and fatty liver disease in US Adults. Dig Liver Dis 2025;57(02):535–541

111. Ashraf MA. Persistent organic pollutants (POPs): a global issue, a global challenge. Environ Sci Pollut Res Int 2017;24(05): 4223–4227 [PubMed: 26370807]

112. Papalou O, Kandaraki EA, Papadakis G, Diamanti-Kandarakis E. Endocrine disrupting chemicals: an occult mediator of metabolic disease. Front Endocrinol (Lausanne) 2019;10:112 [PubMed: 30881345]

113. Guo W, Pan B, Sakkiah S, et al. Persistent organic pollutants in food: contamination sources, health effects and detection methods. Int J Environ Res Public Health 2019;16(22):16

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

114. Wahlang B, Falkner KC, Clair HB, et al. Human receptor activation by aroclor 1260, a polychlorinated biphenyl mixture. Toxicol Sci 2014;140(02):283–297 [PubMed: 24812009]
115. Masuda Y Health status of Japanese and Taiwanese after exposure to contaminated rice oil. Environ Health Perspect 1985; 60:321–325 [PubMed: 3928360]
116. Clair HB, Pinkston CM, Rai SN, et al. Liver disease in a residential cohort with elevated polychlorinated biphenyl exposures. Toxicol Sci 2018;164(01):39–49 [PubMed: 29684222]
117. Kaifie A, Schettgen T, Gube M, Ziegler P, Kraus T, Esser A. Functional and structural liver abnormalities in former PCB exposed workers—analyses from the HELPcB cohort. J Toxicol Environ Health A 2019;82(01):52–61 [PubMed: 30526399]
118. Maroni M, Colombi A, Arbosti G, Cantoni S, Foa V. Occupational exposure to polychlorinated biphenyls in electrical workers. II. Health effects. Br J Ind Med 1981;38(01):55–60 [PubMed: 6451237]
119. Liu Q, Fan G, Bi J, et al. Associations of polychlorinated biphenyls and organochlorine pesticides with metabolic dysfunction-associated fatty liver disease among Chinese adults: effect modification by lifestyle. Environ Res 2024;240(Pt 2):117507 [PubMed: 37918764]
120. Cave MC, Pinkston CM, Rai SN, et al. Circulating microRNAs, polychlorinated biphenyls, and environmental liver disease in the Anniston Community Health Survey. Environ Health Perspect 2022;130(01):17003 [PubMed: 34989596]
121. Hjazi A, Hsu CY, Al-Attar WM, et al. The association of exposure to polychlorinated biphenyls with lipid profile and liver enzymes in umbilical cord blood samples. Chemosphere 2024; 350:141096 [PubMed: 38176591]
122. Midya V, Colicino E, Conti DV, et al. Association of prenatal exposure to endocrine-disrupting chemicals with liver injury in children. JAMA Netw Open 2022;5(07):e2220176 [PubMed: 35793087]
123. Wahlang B RISING STARS: sex differences in toxicant-associated fatty liver disease. J Endocrinol 2023;258(01):258
124. Li MC, Chen PC, Tsai PC, et al. Mortality after exposure to polychlorinated biphenyls and polychlorinated dibenzofurans: a meta-analysis of two highly exposed cohorts. Int J Cancer 2015; 137(06):1427–1432 [PubMed: 25754105]
125. Bertazzi A, Pesatori AC, Consonni D, Tironi A, Landi MT, Zocchetti C. Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. Epidemiology 1993;4 (05):398–406 [PubMed: 8399687]
126. Yi SW, Ohrr H. Agent Orange exposure and cancer incidence in Korean Vietnam veterans: a prospective cohort study. Cancer 2014;120(23):3699–3706 [PubMed: 25103108]
127. Tsai PC, Ko YC, Huang W, Liu HS, Guo YL. Increased liver and lupus mortalities in 24-year follow-up of the Taiwanese people highly exposed to polychlorinated biphenyls and dibenzofurans. Sci Total Environ 2007;374(2–3):216–222 [PubMed: 17257654]
128. VoPham T, Bertrand KA, Fisher JA, Ward MH, Laden F, Jones RR. Emissions of dioxins and dioxin-like compounds and incidence of hepatocellular carcinoma in the United States. Environ Res 2022;204(Pt D):112386 [PubMed: 34800530]
129. Wahlang B, Hardesty JE, Jin J, Falkner KC, Cave MC. Polychlorinated biphenyls and nonalcoholic fatty liver disease. Curr Opin Toxicol 2019;14:21–28 [PubMed: 34485777]
130. Cave MC, Clair HB, Hardesty JE, et al. Nuclear receptors and nonalcoholic fatty liver disease. Biochim Biophys Acta 2016; 1859(09):1083–1099 [PubMed: 26962021]
131. Cano R, Pérez JL, Dávila LA, et al. Role of endocrine-disrupting chemicals in the pathogenesis of non-alcoholic fatty liver disease: a comprehensive review. Int J Mol Sci 2021;22(09):22
132. Lee YM, Jacobs DR Jr, Lee DH. Persistent organic pollutants and type 2 diabetes: a critical review of review articles. Front Endocrinol (Lausanne) 2018;9:712 [PubMed: 30542326]
133. Wahlang B, Falkner KC, Gregory B, et al. Polychlorinated biphenyl 153 is a diet-dependent obesogen that worsens nonalcoholic fatty liver disease in male C57BL6/J mice. J Nutr Biochem 2013; 24(09):1587–1595 [PubMed: 23618531]
134. Wahlang B, Alexander NC II, Li X, Rouchka EC, Kirpich IA, Cave MC. Polychlorinated biphenyls altered gut microbiome in CAR and PXR knockout mice exhibiting toxicant-associated steatohepatitis. Toxicol Rep 2021;8:536–547 [PubMed: 33777700]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

135. Klinge CM, Piell KM, Petri BJ, et al. Combined exposure to polychlorinated biphenyls and high-fat diet modifies the global epitranscriptomic landscape in mouse liver. Environ Epigenet 2021;7(01):dvab008
136. Petri BJ, Piell KM, Wahlang B, et al. Altered splicing factor and alternative splicing events in a mouse model of diet- and polychlorinated biphenyl-induced liver disease. Environ Toxicol Pharmacol 2023;103:104260 [PubMed: 37683712]
137. Wahlang B, Appana S, Falkner KC, McClain CJ, Brock G, Cave MC. Insecticide and metal exposures are associated with a surrogate biomarker for non-alcoholic fatty liver disease in the National Health and Nutrition Examination Survey 2003–2004. Environ Sci Pollut Res Int 2020;27(06):6476–6487 [PubMed: 31873887]
138. Sang H, Lee KN, Jung CH, Han K, Koh EH. Association between organochlorine pesticides and nonalcoholic fatty liver disease in the National Health and Nutrition Examination Survey 2003–2004. Sci Rep 2022;12(01):11590 [PubMed: 35803990]
139. Al-Eryani L, Wahlang B, Falkner KC, et al. Identification of environmental chemicals associated with the development of toxicant-associated fatty liver disease in rodents. Toxicol Pathol 2015;43(04):482–497 [PubMed: 25326588]
140. Ji G, Xu C, Sun H, et al. Organochloride pesticides induced hepatic ABCG5/G8 expression and lipogenesis in Chinese patients with gallstone disease. Oncotarget 2016;7(23):33689–33702 [PubMed: 27203212]
141. Liu Q, Wang Q, Xu C, et al. Organochloride pesticides impaired mitochondrial function in hepatocytes and aggravated disorders of fatty acid metabolism. Sci Rep 2017;7:46339 [PubMed: 28397872]
142. Rantakokko P, Männistö V, Airaksinen R, et al. Persistent organic pollutants and non-alcoholic fatty liver disease in morbidly obese patients: a cohort study. Environ Health 2015;14:79 [PubMed: 26420011]
143. Freire C, Koifman RJ, Koifman S. Hematological and hepatic alterations in Brazilian population heavily exposed to organochlorine pesticides. J Toxicol Environ Health A 2015;78(08): 534–548 [PubMed: 25849770]
144. National Toxicology Program. NTP toxicology and carcinogenesis studies of polybrominated biphenyls (CAS No. 67774-32-7)(Fire-master FF-1(R)) in F344/N rats and B6C3F1 mice (feed studies). Natl Toxicol Program Tech Rep Ser 1993;398:1–235 [PubMed: 12637961]
145. Kling P, Norman A, Andersson PL, Norrgren L, Förlin L. Gender-specific proteomic responses in zebrafish liver following exposure to a selected mixture of brominated flame retardants. Ecotoxicol Environ Saf 2008;71(02):319–327 [PubMed: 18258299]
146. Shockley KR, Cora MC, Malarkey DE, et al. Comparative toxicity and liver transcriptomics of legacy and emerging brominated flame retardants following 5-day exposure in the rat. Toxicol Lett 2020;332:222–234 [PubMed: 32679240]
147. Chen X, Hu G, He B, et al. Effect of brominated flame retardants exposure on liver function and the risk of non-alcoholic fatty liver disease in the US population. Ecotoxicol Environ Saf 2024; 273:116142 [PubMed: 38394757]
148. Zhao X, Chen T, Yang B, et al. Serum levels of novel brominated flame retardants (NBFRs) in residents of a major BFR-producing region: occurrence, impact factors and the relationship to thyroid and liver function. Ecotoxicol Environ Saf 2021;208:111467 [PubMed: 33080422]
149. Guo W, Lei L, Shi X, et al. Nonalcoholic fatty liver disease development in zebrafish upon exposure to bis(2-ethylhexyl)-2,3,4,5-tetrabromophthalate, a novel brominated flame retardant. Environ Sci Technol 2021;55(10):6926–6935 [PubMed: 33938212]
150. Lim JJ, Goedken M, Jin Y, Gu H, Cui JY. Single-cell transcriptomics unveiled that early life BDE-99 exposure reprogrammed the gut-liver axis to promote a proinflammatory metabolic signature in male mice at late adulthood. Toxicol Sci 2024;200(01):114–136 [PubMed: 38648751]
151. Sun Y, Wang Y, Liang B, et al. Hepatotoxicity of decabromodiphenyl ethane (DBDPE) and decabromodiphenyl ether (BDE-209) in 28-day exposed Sprague-Dawley rats. Sci Total Environ 2020;705:135783 [PubMed: 31787299]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

152. Warner GR, Flaws JA. Bisphenol A and phthalates: how environmental chemicals are reshaping toxicology. Toxicol Sci 2018;166 (02):246–249 [PubMed: 30496570]
153. Zou J, Gu Q, Gu D. Association between phthalates exposure and non-alcoholic fatty liver disease under different diagnostic criteria: a cross-sectional study based on NHANES 2017 to 2018. Front Public Health 2024;12:1407976 [PubMed: 39386944]
154. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Division on Earth and Life Studies; Board on Population Health and Public Health Practice; Board on Environmental Studies and Toxicology; Committee on the Guidance on PFAS Testing and Health Outcomes. The National Academies Collection: Reports funded by National Institutes of Health. In: Guidance on PFAS Exposure, Testing, and Clinical Follow-Up. Washington (DC): National Academies Press; 2022
155. Bassler J, Ducatman A, Elliott M, et al. Environmental perfluoroalkyl acid exposures are associated with liver disease characterized by apoptosis and altered serum adipocytokines. Environ Pollut 2019;247:1055–1063 [PubMed: 30823334]
156. Darrow LA, Groth AC, Winquist A, Shin HM, Bartell SM, Steenland K. Modeled perfluorooctanoic acid (PFOA) exposure and liver function in a mid-Ohio valley community. Environ Health Perspect 2016;124(08):1227–1233 [PubMed: 26978841]
157. Mi X, Wu LY, Liu JJ, et al. The effects of Cl-PFESAs exposure on blood lipids—a community-based large population study in Guangzhou. Sci Total Environ 2022;806(Pt 2):150634 [PubMed: 34597565]
158. Consonni D, Fustinoni S. Biochemical and haematological effects of serum PFOA, ADV and cC_6O_4 in workers of a chemical company producing fluoropolymers, Italy, 2013–2022. Int J Hyg Environ Health 2024;262:114440 [PubMed: 39106565]
159. Samala N, Kulkarni M, Lele RS, et al. Associations between per- and polyfluoroalkyl substance exposures and metabolic dysfunction associated steatotic liver disease (MASLD) in adult National Health and Nutrition Examination Survey 2017 to 2018. Toxicol Sci 2024;202(01):142–151 [PubMed: 39150893]
160. Jin R, McConnell R, Catherine C, et al. Perfluoroalkyl substances and severity of nonalcoholic fatty liver in Children: An untargeted metabolomics approach. Environ Int 2020;134:105220 [PubMed: 31744629]
161. Frediani JK, Naioti EA, Vos MB, Figueroa J, Marsit CJ, Welsh JA. Arsenic exposure and risk of nonalcoholic fatty liver disease (NAFLD) among U.S. adolescents and adults: an association modified by race/ethnicity, NHANES 2005–2014. Environ Health 2018;17(01):6 [PubMed: 29334960]
162. Park E, Kim J, Kim B, Park EY. Association between environmental exposure to cadmium and risk of suspected non-alcoholic fatty liver disease. Chemosphere 2021;266:128947 [PubMed: 33220986]
163. Moon MK, Lee I, Lee A, et al. Lead, mercury, and cadmium exposures are associated with obesity but not with diabetes mellitus: Korean National Environmental Health Survey (KoNEHS) 2015–2017. Environ Res 2022;204(Pt A):111888 [PubMed: 34403664]
164. Chung SM, Moon JS, Yoon JS, Won KC, Lee HW. The sex-specific effects of blood lead, mercury, and cadmium levels on hepatic steatosis and fibrosis: Korean nationwide cross-sectional study. J Trace Elem Med Biol 2020;62:126601 [PubMed: 32634767]
165. Wan H, Wang Y, Zhang H, et al. Chronic lead exposure induces fatty liver disease associated with the variations of gut microbiota. Ecotoxicol Environ Saf 2022;232:113257 [PubMed: 35104782]
166. Yang Z, Wu J, Li X, Xie D, Wang Y, Yang T. Association between dietary iron intake and the prevalence of nonalcoholic fatty liver disease: a cross-sectional study. Medicine (Baltimore) 2019;98 (43):e17613 [PubMed: 31651873]
167. Lan Y, Wu S, Wang Y, et al. Association between blood copper and nonalcoholic fatty liver disease according to sex. Clin Nutr 2021; 40(04):2045–2052 [PubMed: 33039155]
168. Sadighara P, Abedini AH, Irshad N, Ghazi-Khansari M, Esrafili A, Yousefi M. Association between non-alcoholic fatty liver disease and heavy metal exposure: a systematic review. Biol Trace Elem Res 2023;201(12):5607–5615 [PubMed: 36929113]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

169. Vethaak AD, Legler J. Microplastics and human health. Science 2021;371(6530):672–674 [PubMed: 33574197]

170. Thompson RC, Olsen Y, Mitchell RP, et al. Lost at sea: where is all the plastic? Science 2004;304(5672):838 [PubMed: 15131299]

171. Cox KD, Covernton GA, Davies HL, Dower JF, Juanes F, Dudas SE. Human consumption of microplastics. Environ Sci Technol 2019; 53(12):7068–7074 [PubMed: 31184127]

172. Karbalaei S, Hanachi P, Walker TR, Cole M. Occurrence, sources, human health impacts and mitigation of microplastic pollution. Environ Sci Pollut Res Int 2018;25(36):36046–36063 [PubMed: 30382517]

173. Zhao B, Rehati P, Yang Z, Cai Z, Guo C, Li Y. The potential toxicity of microplastics on human health. Sci Total Environ 2024; 912:168946 [PubMed: 38043812]

174. Schwabl P, Köppel S, Königshofer P, et al. Detection of various microplastics in human stool: a prospective case series. Ann Intern Med 2019;171(07):453–457 [PubMed: 31476765]

175. Leslie HA, van Velzen MJM, Brandsma SH, Vethaak AD, Garcia-Vallejo JJ, Lamoree MH. Discovery and quantification of plastic particle pollution in human blood. Environ Int 2022;163:107199 [PubMed: 35367073]

176. Saraluck A, Techarang T, Bunyapipat P, Boonchuwong K, Pullaput Y, Mordmuang A. Detection of microplastics in human breast milk and its association with changes in human milk bacterial microbiota. J Clin Med 2024;13(14):13

177. Huang S, Huang X, Bi R, et al. Detection and analysis of microplastics in human sputum. Environ Sci Technol 2022;56(04): 2476–2486 [PubMed: 35073488]

178. Horvatits T, Tamminga M, Liu B, et al. Microplastics detected in cirrhotic liver tissue. EBioMedicine 2022;82:104147 [PubMed: 35835713]

179. Jenner LC, Rotchell JM, Bennett RT, Cowen M, Tentzeris V, Sadofsky LR. Detection of microplastics in human lung tissue using μFTIR spectroscopy. Sci Total Environ 2022;831:154907 [PubMed: 35364151]

180. Yang W, Li Y, Boraschi D. Association between microorganisms and microplastics: how does it change the host-pathogen interaction and subsequent immune response? Int J Mol Sci 2023;24 (04):24

181. Rogers KL, Carreres-Calabuig JA, Gorokhova E, Posth NR. Micro-by-micro interactions: how microorganisms influence the fate of marine microplastics. Limnol Oceanogr Lett 2020;5(1):18–36

182. Prietl B, Meindl C, Roblegg E, Pieber TR, Lanzer G, Fröhlich E. Nano-sized and micro-sized polystyrene particles affect phagocyte function. Cell Biol Toxicol 2014;30(01):1–16 [PubMed: 24292270]

183. Deng Y, Zhang Y, Lemos B, Ren H. Tissue accumulation of microplastics in mice and biomarker responses suggest widespread health risks of exposure. Sci Rep 2017;7:46687 [PubMed: 28436478]

184. Li B, Ding Y, Cheng X, et al. Polyethylene microplastics affect the distribution of gut microbiota and inflammation development in mice. Chemosphere 2020;244:125492 [PubMed: 31809927]

185. Jin Y, Lu L, Tu W, Luo T, Fu Z. Impacts of polystyrene microplastic on the gut barrier, microbiota and metabolism of mice. Sci Total Environ 2019;649:308–317 [PubMed: 30176444]

186. Zhao J, Adiele N, Gomes D, et al. Obesogenic polystyrene microplastic exposures disrupt the gut-liver-adipose axis. Toxicol Sci 2024;198(02):210–220 [PubMed: 38291899]

187. Zhao J, Gomes D, Jin L, et al. Polystyrene bead ingestion promotes adiposity and cardiometabolic disease in mice. Ecotoxicol Environ Saf 2022;232:113239 [PubMed: 35093814]

188. Lu L, Wan Z, Luo T, Fu Z, Jin Y. Polystyrene microplastics induce gut microbiota dysbiosis and hepatic lipid metabolism disorder in mice. Sci Total Environ 2018;631–632:449–458

189. Heudorf U, Mersch-Sundermann V, Angerer J. Phthalates: toxicology and exposure. Int J Hyg Environ Health 2007;210(05): 623–634 [PubMed: 17889607]

190. Rochester JR. Bisphenol A and human health: a review of the literature. Reprod Toxicol 2013;42:132–155 [PubMed: 23994667]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

191. Lioy PJ, Hauser R, Gennings C, et al. Assessment of phthalates/phthalate alternatives in children's toys and childcare articles: review of the report including conclusions and recommendation of the Chronic Hazard Advisory Panel of the Consumer Product Safety Commission. J Expo Sci Environ Epidemiol 2015;25(04):343–353 [PubMed: 25944701]

192. Bornehag CG, Lundgren B, Weschler CJ, Sigsgaard T, Hagerhed-Engman L, Sundell J. Phthalates in indoor dust and their association with building characteristics. Environ Health Perspect 2005; 113(10):1399–1404 [PubMed: 16203254]

193. Wang W, Wu FY, Huang MJ, Kang Y, Cheung KC, Wong MH. Size fraction effect on phthalate esters accumulation, bioaccessibility and in vitro cytotoxicity of indoor/outdoor dust, and risk assessment of human exposure. J Hazard Mater 2013; 261:753–762 [PubMed: 23755845]

194. Lv J, Sun S, Wu R, et al. Phthalate esters in dusts from different indoor and outdoor microenvironment and potential human health risk: a case study in Beijing. Environ Res 2025;266:120513 [PubMed: 39631649]

195. Loganathan SN, Kannan K. Occurrence of bisphenol A in indoor dust from two locations in the eastern United States and implications for human exposures. Arch Environ Contam Toxicol 2011;61(01):68–73 [PubMed: 21221962]

196. Caban M, Stepnowski P. Determination of bisphenol A in size fractions of indoor dust from several microenvironments. Microchem J 2020;153:104392

197. Yu L, Yang M, Cheng M, et al. Associations between urinary phthalate metabolite concentrations and markers of liver injury in the US adult population. Environ Int 2021;155:106608 [PubMed: 33964644]

198. Sun J, Yang S, Zhang Y, Xiang W, Jiang X. Relationship between phthalates exposures and metabolic dysfunction-associated fatty liver disease in United States adults. PLoS One 2024;19(04): e0301097 [PubMed: 38640138]

199. Lang IA, Galloway TS, Scarlett A, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. JAMA 2008;300(11):1303–1310 [PubMed: 18799442]

200. Muncke J Exposure to endocrine disrupting compounds via the food chain: is packaging a relevant source? Sci Total Environ 2009;407(16):4549–4559 [PubMed: 19482336]

201. Benjamin S, Pradeep S, Josh MS, Kumar S, Masai E. A monograph on the remediation of hazardous phthalates. J Hazard Mater 2015;298:58–72 [PubMed: 26004054]

202. Ramadan M, Cooper B, Posnack NG. Bisphenols and phthalates: plastic chemical exposures can contribute to adverse cardiovascular health outcomes. Birth Defects Res 2020;112(17):1362–1385 [PubMed: 32691967]

203. Dueñas-Moreno J, Mora A, Kumar M, Meng XZ, Mahlknecht J. Worldwide risk assessment of phthalates and bisphenol A in humans: the need for updating guidelines. Environ Int 2023; 181:108294 [PubMed: 37935082]

204. Grindler NM, Vanderlinden L, Karthikraj R, et al. Exposure to phthalate, an endocrine disrupting chemical, alters the first trimester placental methylome and transcriptome in women. Sci Rep 2018;8(01):6086 [PubMed: 29666409]

205. Rubin BS. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. J Steroid Biochem Mol Biol 2011; 127(1–2):27–34 [PubMed: 21605673]

206. Eales J, Bethel A, Galloway T, et al. Human health impacts of exposure to phthalate plasticizers: an overview of reviews. Environ Int 2022;158:106903 [PubMed: 34601394]

207. Mondal T, Mondal S, Ghosh SK, et al. Phthalates—a family of plasticizers, their health risks, phytotoxic effects, and microbial bioaugmentation approaches. Environ Res 2022;214(Pt 3):114059 [PubMed: 35961545]

208. Melzer D, Rice NE, Lewis C, Henley WE, Galloway TS. Association of urinary bisphenol a concentration with heart disease: evidence from NHANES 2003/06. PLoS One 2010;5(01):e8673 [PubMed: 20084273]

209. Shankar A, Teppala S. Relationship between urinary bisphenol A levels and diabetes mellitus. J Clin Endocrinol Metab 2011;96 (12):3822–3826 [PubMed: 21956417]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

210. Hatch EE, Nelson JW, Qureshi MM, et al. Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: a cross-sectional study of NHANES data, 1999–2002. Environ Health 2008;7:27 [PubMed: 18522739]
211. Legeay S, Faure S. Is bisphenol A an environmental obesogen? Fundam Clin Pharmacol 2017;31(06):594–609 [PubMed: 28622415]
212. Peng MQ, Karvonen-Gutierrez CA, Herman WH, Mukherjee B, Park SK. Phthalate exposure is associated with more rapid body fat gain in midlife women: The Study of Women's Health Across the Nation (SWAN) Multi-Pollutant Study. Environ Res 2023;216 (Pt 3):114685 [PubMed: 36341787]
213. Agency for Toxic Substances and Disease Registry ((ATSDR)) Toxicological profile for Polycyclic Aromatic Hydrocarbons (PAHs). Atlanta, GA: U.S. Department of Health and Human ServicesPublic Health Service; 1995
214. Xu C, Liu Q, Liang J, et al. Urinary biomarkers of polycyclic aromatic hydrocarbons and their associations with liver function in adolescents. Environ Pollut 2021;278:116842 [PubMed: 33711626]
215. Munir S, Azeem A, Sikandar Zaman M, Zia Ul Haq M. From field to table: ensuring food safety by reducing pesticide residues in food. Sci Total Environ 2024;922:171382 [PubMed: 38432369]
216. World Health Organization. Food and Agriculture Organization of the United Nations. Global Situation of Pesticide Management in Agriculture and Public Health: Report of a 2018 WHO-FAO Survey. Geneva: World Health Organization; 2019
217. Ren XM, Kuo Y, Blumberg B. Agrochemicals and obesity. Mol Cell Endocrinol 2020;515:110926 [PubMed: 32619583]
218. Hansen MRH, Gyawali B, Neupane D, et al. Pesticide exposure and diabetes mellitus in a semi-urban Nepali population: a cross-sectional study. Int Arch Occup Environ Health 2020;93 (04):513–524 [PubMed: 31838733]
219. Czajka M, Matysiak-Kucharek M, Jodłowska-Jędrych B, et al. Organophosphorus pesticides can influence the development of obesity and type 2 diabetes with concomitant metabolic changes. Environ Res 2019;178:108685 [PubMed: 31479978]
220. Petrovova E, Purzyc H, Mazensky D, et al. Morphometric alterations, steatosis, fibrosis and active caspase-3 detection in carbamate bendiocarb treated rabbit liver. Environ Toxicol 2015;30(02):212–222 [PubMed: 23836410]
221. Yang D, Zhang X, Yue L, et al. Thiamethoxam induces nonalcoholic fatty liver disease in mice via methionine metabolism disturb via nicotinamide N-methyltransferase overexpression. Chemosphere 2021;273:129727 [PubMed: 33524747]
222. Séralini G-E, Clair E, Mesnage R, et al. Republished study: long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Environ Sci Eur 2014;26(01):14 [PubMed: 27752412]
223. Thongprakaisang S, Thiantanawat A, Rangkadilok N, Suriyo T, Satayavivad J. Glyphosate induces human breast cancer cells growth via estrogen receptors. Food Chem Toxicol 2013;59:129–136 [PubMed: 23756170]
224. Mesnage R, Arno M, Costanzo M, Malatesta M, Séralini GE, Antoniou MN. Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure. Environ Health 2015;14:70 [PubMed: 26302742]
225. Eskenazi B, Gunier RB, Rauch S, et al. Association of lifetime exposure to glyphosate and aminomethylphosphonic acid (AMPA) with liver inflammation and metabolic syndrome at young adulthood: findings from the CHAMACOS Study. Environ Health Perspect 2023;131(03):37001 [PubMed: 36856429]
226. Kwon HC, Sohn H, Kim DH, Jeong CH, Kim DW, Han SG. Effects of flutriafol fungicide on the lipid accumulation in human liver cells and rat liver. Foods 2021;10(06):10
227. Pirozzi AV, Stellavato A, La Gatta A, Lamberti M, Schiraldi C. Mancozeb, a fungicide routinely used in agriculture, worsens nonalcoholic fatty liver disease in the human HepG2 cell model. Toxicol Lett 2016;249:1–4 [PubMed: 27016407]

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228. Xiao S, Cui J, Chen A, et al. Thyroid dysfunction induced by fungicide famoxadone exposure contributes to nonalcoholic fatty liver disease in male mice: in vivo, in vitro, and in silico studies. Environ Sci Technol 2023;57(40):14881–14891 [PubMed: 37749806]

229. Arshad H, Mehmood MZ, Shah MH, Abbasi AM. Evaluation of heavy metals in cosmetic products and their health risk assessment. Saudi Pharm J 2020;28(07):779–790 [PubMed: 32647479]

230. Balwierz R, Biernat P, Jasińska-Balwierz A, et al. Potential carcinogens in makeup cosmetics. Int J Environ Res Public Health 2023;20(06):4780 [PubMed: 36981689]

231. Klančič V, Gobec M, Jakopin Ž Environmental contamination status with common ingredients of household and personal care products exhibiting endocrine-disrupting potential. Environ Sci Pollut Res Int 2022;29(49):73648–73674 [PubMed: 36083363]

232. Acir IH, Guenther K. Endocrine-disrupting metabolites of alkylphenol ethoxylates—a critical review of analytical methods, environmental occurrences, toxicity, and regulation. Sci Total Environ 2018;635:1530–1546 [PubMed: 29874777]

233. Casale T, Caciari T, Rosati MV, et al. Liver function in workers exposed of the cosmetics industry. Ann Ig 2013;25(06):519–527 [PubMed: 24284538]

234. Alnuqaydan AM. The dark side of beauty: an in-depth analysis of the health hazards and toxicological impact of synthetic cosmetics and personal care products. Front Public Health 2024; 12:1439027 [PubMed: 39253281]

235. Patel S Fragrance compounds: the wolves in sheep's clothings. Med Hypotheses 2017;102:106–111 [PubMed: 28478814]

236. Schnell S, Bols NC, Barata C, Porte C. Single and combined toxicity of pharmaceuticals and personal care products (PPCPs) on the rainbow trout liver cell line RTL-W1. Aquat Toxicol 2009;93(04): 244–252 [PubMed: 19500862]

237. Schnell S, Martin-Skilton R, Fernandes D, Porte C. The interference of nitro- and polycyclic musks with endogenous and xenobiotic metabolizing enzymes in carp: an in vitro study. Environ Sci Technol 2009;43(24):9458–9464 [PubMed: 19928757]

238. Politano VT, Lapczynski AA, Ritacco G, Api AM. Ninety-day toxicity study of alpha-iso-methylionone in rats. Int J Toxicol 2012;31(06):595–601 [PubMed: 23283689]

239. Newcombe G, Chorus I, Falconer I, Lin TF. Cyanobacteria: impacts of climate change on occurrence, toxicity and water quality management. Water Res 2012;46(05):1347–1348 [PubMed: 22265251]

240. Li T, Fan X, Cai M, et al. Advances in investigating microcystin-induced liver toxicity and underlying mechanisms. Sci Total Environ 2023;905:167167 [PubMed: 37730048]

241. Zhang F, Lee J, Liang S, Shum CK. Cyanobacteria blooms and non-alcoholic liver disease: evidence from a county level ecological study in the United States. Environ Health 2015;14:41 [PubMed: 25948281]

242. Stahre M, Roeber J, Kanny D, Brewer RD, Zhang X. Contribution of excessive alcohol consumption to deaths and years of potential life lost in the United States. Prev Chronic Dis 2014;11:E109 [PubMed: 24967831]

243. King L, Aplin R, Gill C, Naimi T. A state-of-the-science review of alcoholic beverages and polycyclic aromatic hydrocarbons. Environ Health Perspect 2024;132(01):16001 [PubMed: 38241192]

244. Lotti M Do occupational exposures to vinyl chloride cause hepatocellular carcinoma and cirrhosis? Liver Int 2017;37(05): 630–633 [PubMed: 28063180]

245. Yang J, Zhang L, Wang T, et al. Synergistic effects of combined treatment of 1,2-dichloroethane and high-dose ethanol on liver damage in mice and the related mechanisms. Food Chem Toxicol 2023;176:113812 [PubMed: 37150348]

246. Gripshover TC, Wahlang B, Head KZ, et al. Multiomics analysis of PCB126's effect on a mouse chronic-binge alcohol feeding model. Environ Health Perspect 2024;132(04):47007 [PubMed: 38619879]

247. Gripshover TC, Wahlang B, Head KZ, et al. The environmental pollutant, polychlorinated biphenyl 126, alters liver function in a rodent model of alcohol-associated liver disease. Alcohol Clin Exp Res (Hoboken) 2023;47(01):60–75 [PubMed: 36377258]

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248. Mailloux RJ, Florian M, Chen Q, et al. Exposure to a northern contaminant mixture (NCM) alters hepatic energy and lipid metabolism exacerbating hepatic steatosis in obese JCR rats. PLoS One 2014;9(09):e106832 [PubMed: 25222487]

249. Ding S, Jiang J, Zhang G, Yu M, Zheng Y. Ambient particulate matter exposure plus chronic ethanol ingestion exacerbates hepatic fibrosis by triggering the mitochondrial ROS-ferroptosis signaling pathway in mice. Ecotoxicol Environ Saf 2023; 256:114897 [PubMed: 37043943]

250. Petrescu AD, Venter J, Danilenko DD, et al. Exposure to Gulf war illness-related chemicals exacerbates alcohol-induced liver damage in rodents. Sci Rep 2024;14(01):14981 [PubMed: 38951546]

251. Joshi-Barve S, Amancherla K, Patil M, et al. Acrolein, a ubiquitous pollutant and lipid hydroperoxide product, inhibits antiviral activity of interferon-alpha: relevance to hepatitis C. Free Radic Biol Med 2009;47(01):47–54 [PubMed: 19345260]

252. Gershwin ME, Selmi C, Worman HJ, et al. ; USA PBC Epidemiology Group. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. Hepatology 2005;42(05):1194–1202 [PubMed: 16250040]

253. Juran BD, Lazaridis KN. Environmental factors in primary biliary cirrhosis. Semin Liver Dis 2014;34(03):265–272 [PubMed: 25057950]

254. Dyson JK, Blain A, Foster Shirley MD, Hudson M, Rushton S, Jeffreys Jones DE. Geo-epidemiology and environmental co-variate mapping of primary biliary cholangitis and primary sclerosing cholangitis. JHEP Rep Innov Hepatol 2020;3(01): 100202

255. Ala A, Stanca CM, Bu-Ghanim M, et al. Increased prevalence of primary biliary cirrhosis near Superfund toxic waste sites. Hepatology 2006;43(03):525–531 [PubMed: 16496326]

256. Sargis RM, Heindel JJ, Padmanabhan V. Interventions to address environmental metabolism-disrupting chemicals: changing the narrative to empower action to restore metabolic health. Front Endocrinol (Lausanne) 2019;10:33 [PubMed: 30778334]

257. Guzelian PS. Therapeutic approaches for chlordecone poisoning in humans. J Toxicol Environ Health 1981;8(5–6):757–766 [PubMed: 6175768]

258. Jandacek RJ, Heubi JE, Buckley DD, et al. Reduction of the body burden of PCBs and DDE by dietary intervention in a randomized trial. J Nutr Biochem 2014;25(04):483–488 [PubMed: 24629911]

259. Mengozzi A, Carli F, Guiducci L, et al. SGLT2 inhibitors and thiazide enhance excretion of DEHP toxic metabolites in subjects with type 2 diabetes: a randomized clinical trial. Environ Res 2021;192:110316 [PubMed: 33065070]

260. Takasuga T, Senthilkumar K, Takemori H, Ohi E, Tsuji H, Nagayama J. Impact of FEBRA (fermented brown rice with Aspergillus oryzae) intake and concentrations of PCDDs, PCDFs and PCBs in blood of humans from Japan. Chemosphere 2004;57 (10):1409–1426 [PubMed: 15519386]

261. The National Academies of Sciences. Engineering, and Medicine. Guidance on PFAS Exposure, Testing, and Clinical Follow-Up. Washington, DC: The National Academies Press; 2022

262. Rinella ME, Lazarus JV, Ratziu V, et al. ; NAFLD Nomenclature Consensus Group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Ann Hepatol 2024;29(01): 101133 [PubMed: 37364816]

263. Li R, Sun Q, Lam SM, et al. Sex-dependent effects of ambient $PM_{2.5}$ pollution on insulin sensitivity and hepatic lipid metabolism in mice. Part Fibre Toxicol 2020;17(01):14 [PubMed: 32321544]

264. Deng P, Tang H, Zhu L, et al. Association of long-term ambient fine particulate matter ($PM_{2.5}$) and incident non-alcoholic fatty liver disease in Chinese adults. Environ Pollut 2023;329:121666 [PubMed: 37080516]

265. Markevych I, Wolf K, Hampel R, et al. Air pollution and liver enzymes. Epidemiology 2013;24(06):934–935 [PubMed: 24076996]

266. Fedeli U, Girardi P, Mastrangelo G. Occupational exposure to vinyl chloride and liver diseases. World J Gastroenterol 2019;25 (33):4885–4891 [PubMed: 31543680]

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267. Luo J, Watson WH, Gripshover TC, Qaissi Z, Wahlang B. Sex-specific effects of acute chlordane exposure in the context of steatotic liver disease, energy metabolism and endocrine disruption. Food Chem Toxicol 2023;180:114024 [PubMed: 37666290]

268. Zhang Y, Lu M, Zhou P, Wang C, Zhang Q, Zhao M. Multilevel evaluations of potential liver injury of bifenthrin. Pestic Biochem Physiol 2015;122:29–37 [PubMed: 26071804]

269. Averina M, Huber S, Almås B, et al. Early menarche and other endocrine disrupting effects of per- and polyfluoroalkyl substances (PFAS) in adolescents from Northern Norway. The Fit Futures study. Environ Res 2024;242:117703 [PubMed: 37984785]

270. Men H, Young JL, Zhou W, et al. Early-life exposure to low-dose cadmium accelerates diethylnitrosamine and diet-induced liver cancer. Oxid Med Cell Longev 2021;2021:1427787 [PubMed: 34876963]

271. Tinkov AA, Aschner M, Santamaria A, et al. Dissecting the role of cadmium, lead, arsenic, and mercury in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Environ Res 2023;238 (Pt 1):117134 [PubMed: 37714366]

272. Coradduzza D, Congiargiu A, Azara E, et al. Heavy metals in biological samples of cancer patients: a systematic literature review. Biometals 2024;37(04):803–817 [PubMed: 38347295]

273. Hyder O, Chung M, Cosgrove D, et al. Cadmium exposure and liver disease among US adults. J Gastrointest Surg 2013;17(07): 1265–1273 [PubMed: 23636881]

274. Hardesty JE, Al-Eryani L, Wahlang B, et al. Epidermal growth factor receptor signaling disruption by endocrine and metabolic disrupting chemicals. Toxicol Sci 2018;162(02):622–634 [PubMed: 29329451]

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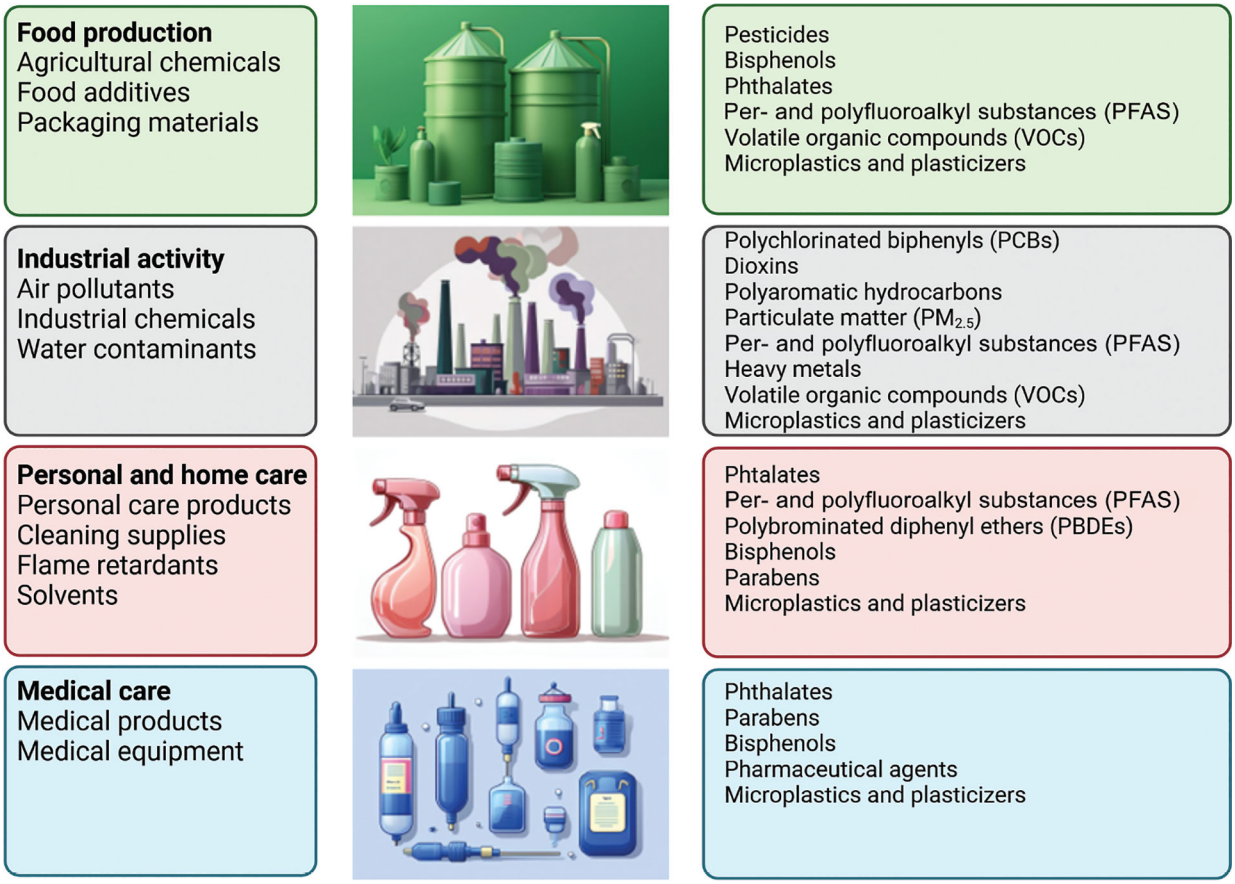

Fig. 1. Sources and pathways of environmental liver toxicants.

Major exposure sources that can impact liver health include food production (green), industrial activity (gray), personal and home care products (pink), and medical care (blue). Many compounds, such as per- and polyfluoroalkyl substances (PFAS), phthalates, and bisphenols derive from multiple sources, highlighting their pervasive presence in commonly used products and environmental media. (Created with BioRender.com.)

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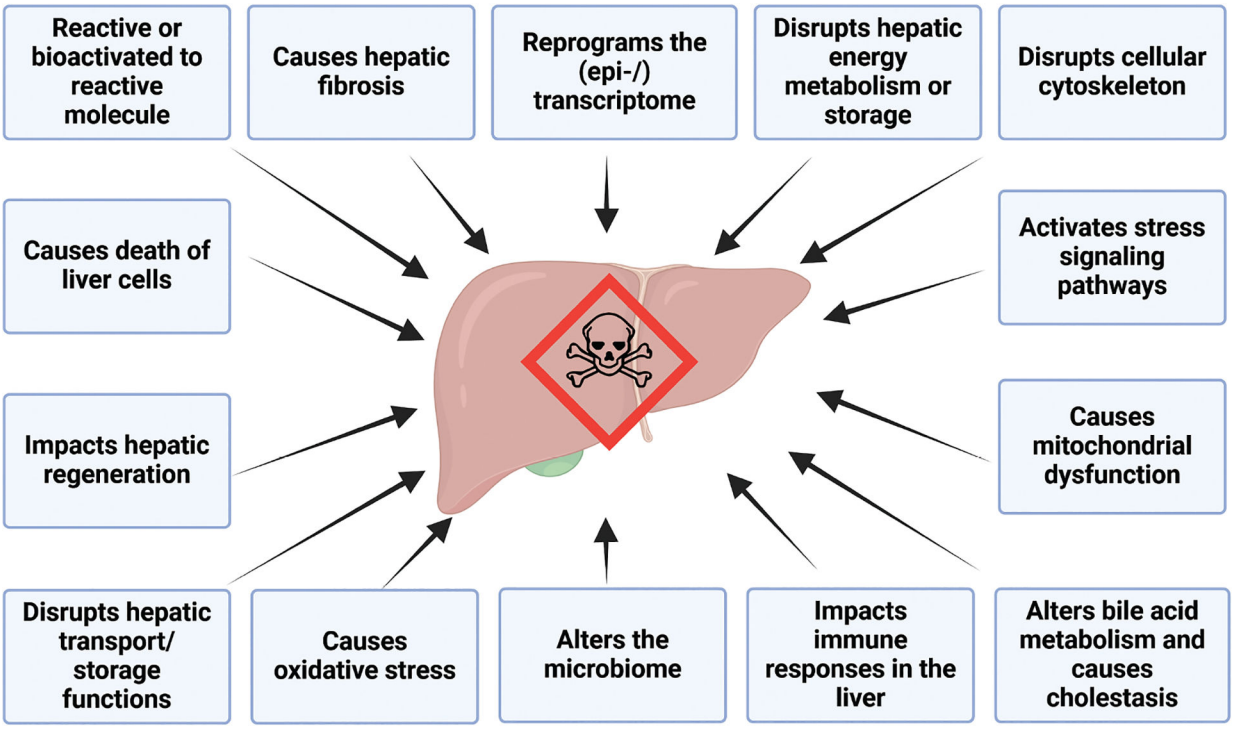
Reactive or bioactivated to reactive molecule
Causes hepatic fibrosis
Reprograms the (epi-/) transcriptome
Disrupts hepatic energy metabolism or storage
Disrupts cellular cytoskeleton
Causes death of liver cells
Activates stress signaling pathways
Impacts hepatic regeneration
Causes mitochondrial dysfunction
Disrupts hepatic transport/ storage functions
Causes oxidative stress
Alters the microbiome
Impacts immune responses in the liver
Alters bile acid metabolism and causes cholestasis

Fig. 2. Overview of hepatotoxic mechanisms.

Schematic representation of the major pathways through which hepatotoxicants can cause liver injury. These mechanisms include structural alterations (disruption of cellular cytoskeleton), metabolic perturbations (energy and bile acid metabolism, mitochondrial function), inflammatory responses (immune system activation), cell death, transport dysfunction, oxidative damage, transcriptional reprogramming, altered microbiome, and tissue remodeling (fibrosis). Hepatotoxicants can act through one or multiple pathways simultaneously, leading to various manifestations of liver injury. The central illustration depicts the liver, with arrows indicating the convergence of these diverse pathogenic mechanisms. (Created with BioRender.com.)

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Table 1

Environmental and occupational chemicals and associated liver disease and mechanisms

Category of the Exposure		Associated liver disease	Mechanisms /Animal study	Clinical index/Epidemiological study
Air pollutants	PM2.5	MASLD, ↑increased hospitalization, TAFLD	TAFLD[263]	Associated with MASLD,[100,264] ↑GGT[265]
	Vinyl chloride	Angiosarcoma[49,54–56] HCC,[56] MASLD[41,110]	↑ROS[53,103]	Increased mortality from HCC[266] ↑ALT, ↑AST[92]
Aflatoxin B		HCC[60,61]		
Dioxin	TCDD/PCDFS/dioxin-like PCBs	HCC, cirrhosis, SLD		↑Incidence of HCC and mortality[124] Cirrhosis[124]
Brominated flame retardants (BFR)	PBDE/BTPDE/DEHP	MASLD	(+) PPARa Gut microbiome change Inflammation ROS	↑ALT, ↑AST, ↑GGT,[147] ↑ALT, ↑Bilirubin[148]
Pesticide	DTT Organochlorine Organophosphorus Carbamates Pyrethroids Neonicotinoids	SLD, MASLD PSC, PBC[43]	↑ROS[76] EDC, MDC[267] MDC[268] Dyslipidemia[221]	↑Tumor biomarkers[78] ↑Liver enzymes[137] Association with obesity DM2[219] PSC, PBC[43]
Fungicide	Triazole (Flutriafol) Oxazolidinedione (Famoxadone)	↑ MASLD risk SLD, MASLD	↑Lipid accumulation[226] EDC, ↓ lipid oxidation[228]	
Herbicide	Glyphosate (Roundup)	Liver injury and metabolic syndrome	↑Liver congestion and mortality[222] EDC[224]	↑Liver enzymes, ↑metabolic syndrome[225]
Personal care products/ Cosmetic products	Parabens Alkylphenol ethoxylates Synthetic musk	SLD	EDC ↓ AST ↑liver weight ↑cholesterol, ↑creatinine[238]	
Microplastic/Plasticizers	Phthalates/ Bisphenol A (BPA) / Polystyrene	MASLD	Induce inflammatory,[184] EDC[204]↑ROS[183]	Obesity[187]
PFAS	PFOA/PFOS		Altered androgen[269]	↓ Liver function[12]
Heavy metals	Arsenic	HCC,[270] MASLD[161]	↑ Cancer growth and metastasis[87] ↑ Steatosis, inflammation[271]	HCC[29] Stronger association of HCC with female[88]
	Cadmium	↑Risk of HCC MASLD[163]	↑ HCC risk[270]↑	Linked to tumor formation,[272] liver disease mortality[273]
PCBs	TASLD[115]	HCC[73]	EDC, MDC, (+) AHR (+) CAR,[132] (−) EGFR[274]	HCC,[74]↑ALT, ↑AST, ↑CK18[116–120]
Miscellaneous	Microcystins	SLD, acute liver failure or chronic liver injury[241]		↑MASLD[241]

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BTPDE, dichlorodiphenyltrichloroethane; DDT, dichlorodiphenyltrichloroethane; DEHP, di(2-ethylhexyl) phthalate; EDC, endocrine disrupting chemical; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MDC, metabolism disrupting chemical; PBDE, polybrominated diphenyl ethers; PCB, polychlorinated biphenyl; PCDFS, polychlorinated dibenzofurans; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PSC, primary sclerosing cholangitis; ROS, reactive oxygen species; SLD, steatotic liver disease; TAFLD, toxicant-associated fatty liver disease; TASLD, toxicant-associated steatotic liver disease; TCDD, tetrachlorodibenzo-p-dioxin.

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Table 2

Impact of environmental exposures on alcohol-associated liver disease in animalmodels: Summary of recent studies examining the interaction between environmental toxicants and alcohol consumption in rodent models

Environmental exposure	Animal model	Study duration	Key findings	Mechanisms	Reference
1,2-Dichloroethane (1,2-DCE)	Female Kunming mice	6 days EtOH (1.5–3.0 g/kg) + 3 days 1,2-DCE (1.0 mg/L, 3.5 h/day inhalation)	• ↑ Liver damage • ↑ CYP2E1 expression • ↑ Inflammatory response • ↑ Antioxidant defense	• ↑ CYP2E1-mediated oxidative stress • ↑ NLRP3 inflammasome activation • Insufficient antioxidant compensation • Confirmed via CYP2E1 inhibition	70
Ambient particulate matter (PM)	Male C57BL/6 mice	12 weeks	• ↑ Liver fibrosis • ↑ Hepatic oxidative stress • ↑ Mitochondrial ROS • ↑ Hepatic ferroptosis	• ↑ ROS-ferroptosis pathway • ↑ TGF-β1/collagen-I • Altered GSH/GSSG ratio • Stellate cell activation	249
Gulf War Illness-related chemicals (Permethrin + Pyridostigmine-bromide)	Male C57BL/6 mice	10 days exposure + 4 months recovery + 10 days EtOH challenge	• ↑ Microvesicular steatosis ↑ Chronic inflammation ↑ Liver fibrosis ↑ Liver enzymes	• Macrophage-mediated damage • Prolonged liver sensitization • Enhanced inflammatory response	250
Polychlorinated biphenyl 126 (PCB126)	Male C57BL/6J mice	Single exposure (0.2 mg/kg) + chronic-binge alcohol model	• ↑ Hepatic steatosis • ↑ Hepatomegaly • ↓ Albumin levels • ↓ Glycogen stores	• ↑ Lipid retention • ↓ Lipid oxidation • AHR/CAR activation • Enhanced malnutrition	247
Polychlorinated biphenyl 126 (PCB126)	Male C57BL/6J mice	Single exposure (0.2 mg/kg) + chronic-binge alcohol model	• Altered transcriptome ↓ Metal homeostasis • ↓ Essential metals • Modified metabolism	• >4,000 altered genes • ↓ Mg, Co, Zn levels • Modified tyrosine pathways	246

Abbreviations: AHR, aryl hydrocarbon receptor; CAR, constitutive androstane receptor.